CS481: Bioinformatics Algorithms

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Quiz 1: DNA mapping

$\Delta X = \{0,1,2,3,3,5,5,7,8,8,10,12,13,13,15,16\}$

X = {0, 16} check 15 and 16-15=1 **Δ(15, X) = Δ(1, X) = {15, 1)**
pick either 15 or 1; remove 1 and 15 from ΔX

X = {0, 15, 16} L= {2,3,3,5,5,7,8,8,10,12,13,13}
check 13 and 3; **Δ(13, X)={13,2,3} subset of L**

X = {0, 13, 15, 16} L = {3,5,5,7,8,8,10,12,13}
check 13 and 3; **Δ(13, X)={13,0,2,3} not subset of L**
Δ(3, X)={3,10,12,13} subset of L

X = {0, 3, 13, 15, 16} L = {5,5,7,8,8}
check 8; **Δ(8, X)={8,5,5,7,8} subset of L**

X = {0, 3, 8, 13, 15, 16} L = {} done

Alternative: ***X = {0, 1, 3, 8, 13, 16}***

MORE ON PAIRWISE ALIGNMENT

From LCS to Alignment: Change up the Scoring

- The Longest Common Subsequence (LCS) problem—the simplest form of sequence alignment – allows only insertions and deletions (no mismatches).
- In the LCS Problem, we scored 1 for matches and 0 for indels
- Consider penalizing indels and mismatches with negative scores
- Simplest *scoring schema*:

  $+1$: **match premium**

  $-\mu$: **mismatch penalty**

  $-\sigma$: **indel penalty**

Simple Scoring

- When mismatches are penalized by $-\mu$, indels are penalized by $-\sigma$,

  and matches are rewarded with $+1$,

  the resulting score is:

$$\#matches - \mu(\#mismatches) - \sigma\ (\#indels)$$

The Global Alignment Problem

Find the best alignment between two strings under a given scoring schema

Input : Strings **v** and **w** and a scoring schema
Output : Alignment of maximum score

$\uparrow \rightarrow = -\sigma$

$\searrow$ $= 1$ if match
$= -\mu$ if mismatch

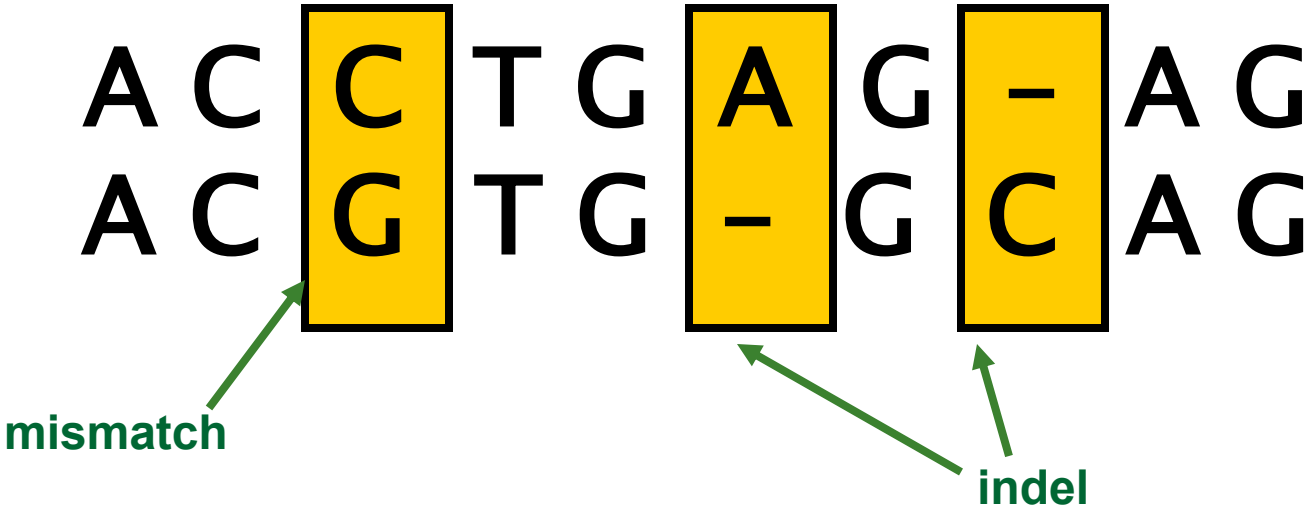
$$s_{i,j} = \max \begin{cases} s_{i-1,j-1} + 1 & \text{if } v_i = w_j \\ s_{i-1,j-1} - \mu & \text{if } v_i \neq w_j \\ s_{i-1,j} - \sigma \\ s_{i,j-1} - \sigma \end{cases}$$

μ : mismatch penalty
σ : indel penalty

Needleman-Wunsch algorithm

Percent Sequence Identity

- The extent to which two nucleotide or amino acid sequences are invariant



Alignment length = 10
Matches = 7
70% identical

Similarity vs. identity

- Common usage:
  - *Similarity* for amino acid alignments (protein-protein)
  - *Identity* for nucleotide alignments (DNA-DNA or RNA-RNA)

Scoring Matrices

To generalize scoring, consider a (4+1) x(4+1) **scoring matrix** δ.

In the case of an amino acid sequence alignment, the scoring matrix would be a (20+1)x(20+1) size. The addition of 1 is to include the score for comparison of a gap character "-".

This will simplify the algorithm as follows:

$$s_{i,j} = max \begin{cases} s_{i-1,j-1} + \delta(v_i, w_j) \\ s_{i-1,j} + \delta(v_i, -) \\ s_{i,j-1} + \delta(-, w_j) \end{cases}$$

Making a Scoring Matrix

- Scoring matrices are created based on biological evidence.
- Alignments can be thought of as two sequences that differ due to mutations.
- Some of these mutations have little effect on the protein's function, therefore some penalties, $\delta(v_i , w_j)$, will be less harsh than others.

Scoring Matrix: Example

	A	R	N	K
A	5	-2	-1	-1
R	-	7	-1	3
N	-	-	7	0
K	-	-	-	6

AKRANR

KAAANK

-1 + (-1) + (-2) + 5 + 7 + 3 = 11

- Notice that although R and K are different amino acids, they have a positive score.
- Why? They are both positively charged amino acids→ will not greatly change function of protein.

Conservation

- Amino acid changes that tend to preserve the physico-chemical properties of the original residue
  - Polar to polar
    - aspartate → glutamate
  - Nonpolar to nonpolar
    - alanine → valine
  - Similarly behaving residues
    - leucine to isoleucine

Scoring matrices

- Amino acid substitution matrices
  - PAM
  - BLOSUM
- DNA substitution matrices
  - DNA is less conserved than protein sequences
  - Less effective to compare coding regions at nucleotide level

PAM

- **P**oint **A**ccepted **M**utation (Dayhoff et al.)
- PAM_{250} is a widely used scoring matrix:

	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	...
	A	R	N	D	C	Q	E	G	H	I	L	K	...
Ala A	13	6	9	9	5	8	9	12	6	8	6	7	...
Arg R	3	17	4	3	2	5	3	2	6	3	2	9	
Asn N	4	4	6	7	2	5	6	4	6	3	2	5	
Asp D	5	4	8	11	1	7	10	5	6	3	2	5	
Cys C	2	1	1	1	52	1	1	2	2	2	1	1	
Gln Q	3	5	5	6	1	10	7	3	7	2	3	5	
...													
Trp W	0	2	0	0	0	0	0	0	1	0	1	0	
Tyr Y	1	1	2	1	3	1	1	1	3	2	2	1	
Val V	7	4	4	4	4	4	4	4	5	4	15	10	

BLOSUM

- **Blo**cks **Su**bstitution **M**atrix
- Scores derived from *observations* of the frequencies of substitutions in blocks of local alignments in related proteins
- Matrix name indicates evolutionary distance
  - BLOSUM62 was created using sequences sharing no more than 62% identity

The Blosum50 Scoring Matrix

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V	B	Z	X	*
A	5	-2	-1	-2	-1	-1	-1	0	-2	-1	-2	-1	-1	-3	-1	1	0	-3	-2	0	-2	-1	-1	-5
R	-2	7	-1	-2	-4	1	0	-3	0	-4	-3	3	-2	-3	-3	-1	-1	-3	-1	-3	-1	0	-1	-5
N	-1	-1	7	2	-2	0	0	0	1	-3	-4	0	-2	-4	-2	1	0	-4	-2	-3	4	0	-1	-5
D	-2	-2	2	8	-4	0	2	-1	-1	-4	-4	-1	-4	-5	-1	0	-1	-5	-3	-4	5	1	-1	-5
C	-1	-4	-2	-4	13	-3	-3	-3	-3	-2	-2	-3	-2	-2	-4	-1	-1	-5	-3	-1	-3	-3	-2	-5
Q	-1	1	0	0	-3	7	2	-2	1	-3	-2	2	0	-4	-1	0	-1	-1	-1	-3	0	4	-1	-5
E	-1	0	0	2	-3	2	6	-3	0	-4	-3	1	-2	-3	-1	-1	-1	-3	-2	-3	1	5	-1	-5
G	0	-3	0	-1	-3	-2	-3	8	-2	-4	-4	-2	-3	-4	-2	0	-2	-3	-3	-4	-1	-2	-2	-5
H	-2	0	1	-1	-3	1	0	-2	10	-4	-3	0	-1	-1	-2	-1	-2	-3	2	-4	0	0	-1	-5
I	-1	-4	-3	-4	-2	-3	-4	-4	-4	5	2	-3	2	0	-3	-3	-1	-3	-1	4	-4	-3	-1	-5
L	-2	-3	-4	-4	-2	-2	-3	-4	-3	2	5	-3	3	1	-4	-3	-1	-2	-1	1	-4	-3	-1	-5
K	-1	3	0	-1	-3	2	1	-2	0	-3	-3	6	-2	-4	-1	0	-1	-3	-2	-3	0	1	-1	-5
M	-1	-2	-2	-4	-2	0	-2	-3	-1	2	3	-2	7	0	-3	-2	-1	-1	0	1	-3	-1	-1	-5
F	-3	-3	-4	-5	-2	-4	-3	-4	-1	0	1	-4	0	8	-4	-3	-2	1	4	-1	-4	-4	-2	-5
P	-1	-3	-2	-1	-4	-1	-1	-2	-2	-3	-4	-1	-3	-4	10	-1	-1	-4	-3	-3	-2	-1	-2	-5
S	1	-1	1	0	-1	0	-1	0	-1	-3	-3	0	-2	-3	-1	5	2	-4	-2	-2	0	0	-1	-5
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	2	5	-3	-2	0	0	-1	0	-5
W	-3	-3	-4	-5	-5	-1	-3	-3	-3	-3	-2	-3	-1	1	-4	-4	-3	15	2	-3	-5	-2	-3	-5
Y	-2	-1	-2	-3	-3	-1	-2	-3	2	-1	-1	-2	0	4	-3	-2	-2	2	8	-1	-3	-2	-1	-5
V	0	-3	-3	-4	-1	-3	-3	-4	-4	4	1	-3	1	-1	-3	-2	0	-3	-1	5	-4	-3	-1	-5
B	-2	-1	4	5	-3	0	1	-1	0	-4	-4	0	-3	-4	-2	0	0	-5	-3	-4	5	2	-1	-5
Z	-1	0	0	1	-3	4	5	-2	0	-3	-3	1	-1	-4	-1	0	-1	-2	-2	-3	2	5	-1	-5
X	-1	-1	-1	-1	-2	-1	-1	-2	-1	-1	-1	-1	-1	-2	-2	-1	0	-3	-1	-1	-1	-1	-1	-5
*	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	1

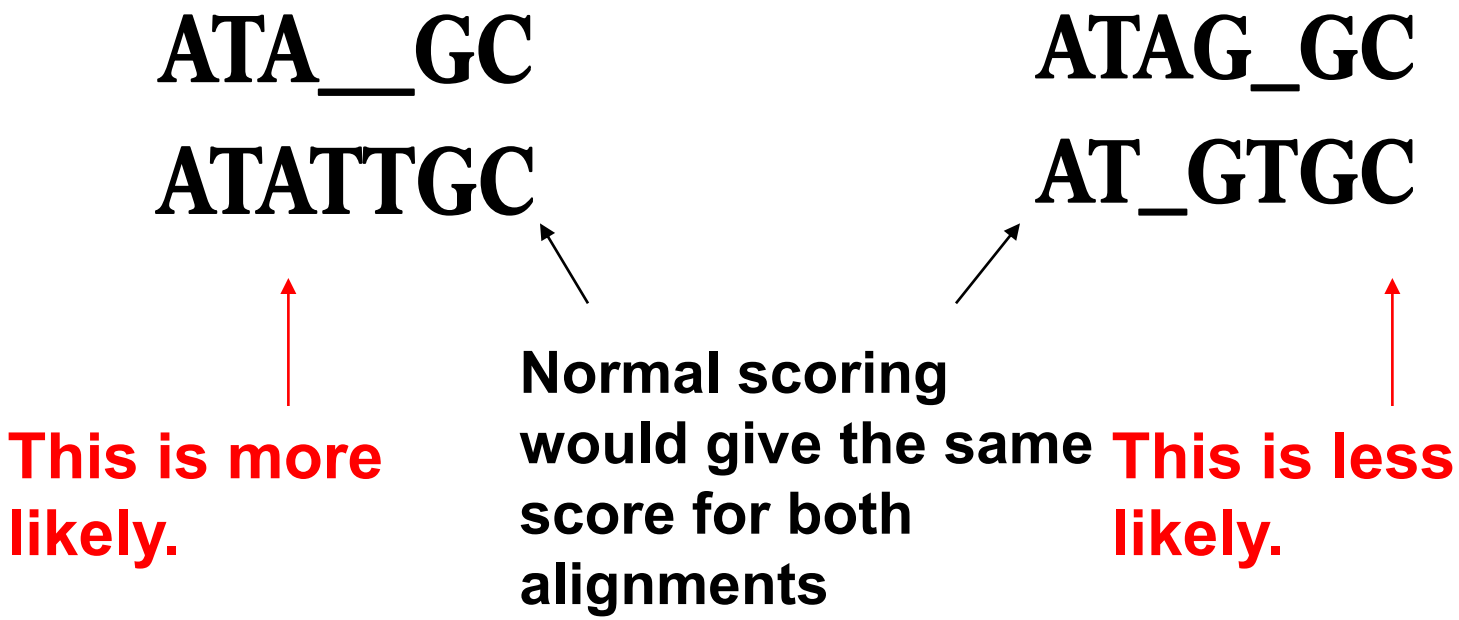
Scoring Indels: Naive Approach

- A fixed penalty σ is given to every indel:
  - $-\sigma$ for 1 indel,
  - -2σ for 2 consecutive indels
  - -3σ for 3 consecutive indels, etc.

Can be too severe penalty for a series of 100 consecutive indels

Affine Gap Penalties

- In nature, a series of *k* indels often come as a single event rather than a series of *k* single nucleotide events:



Accounting for Gaps

- *Gaps*- contiguous sequence of spaces in one of the rows

- Score for a gap of length x is:

  $$-(\rho + \sigma x)$$

  where $\rho > 0$ is the penalty for introducing a gap:

  gap opening penalty

  ρ will be large relative to σ:

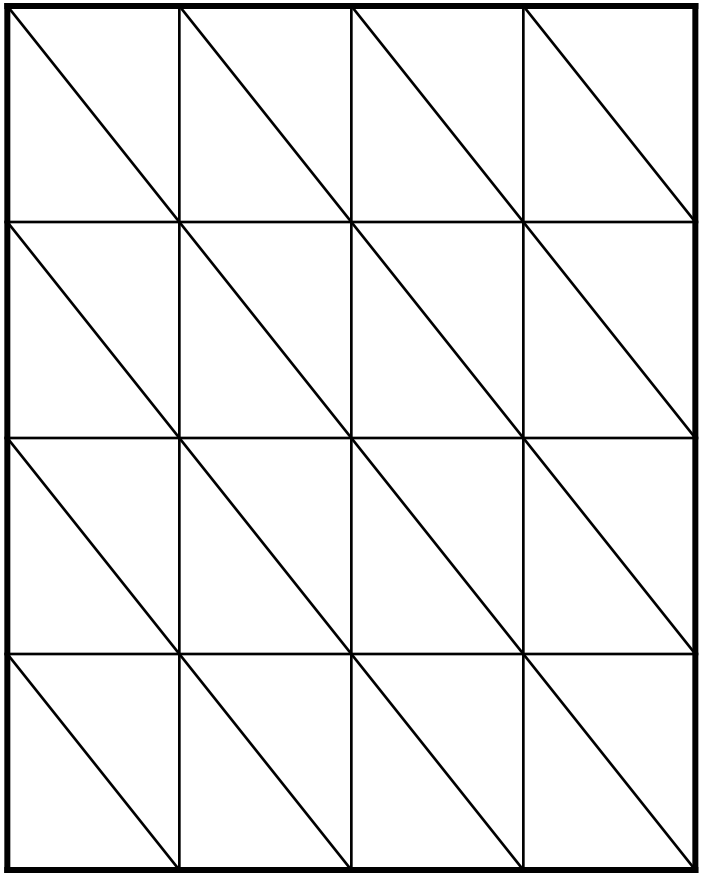
  gap extension penalty

  because you do not want to add too much of a penalty for extending the gap.

Affine Gap Penalties

- Gap penalties:
  - $-\rho-\sigma$ when there is 1 indel
  - $-\rho-2\sigma$ when there are 2 indels
  - $-\rho-3\sigma$ when there are 3 indels, etc.
  - $-\rho- x \cdot \sigma$ (-gap opening - x gap extensions)
- Somehow reduced penalties (as compared to naïve scoring) are given to runs of horizontal and vertical edges

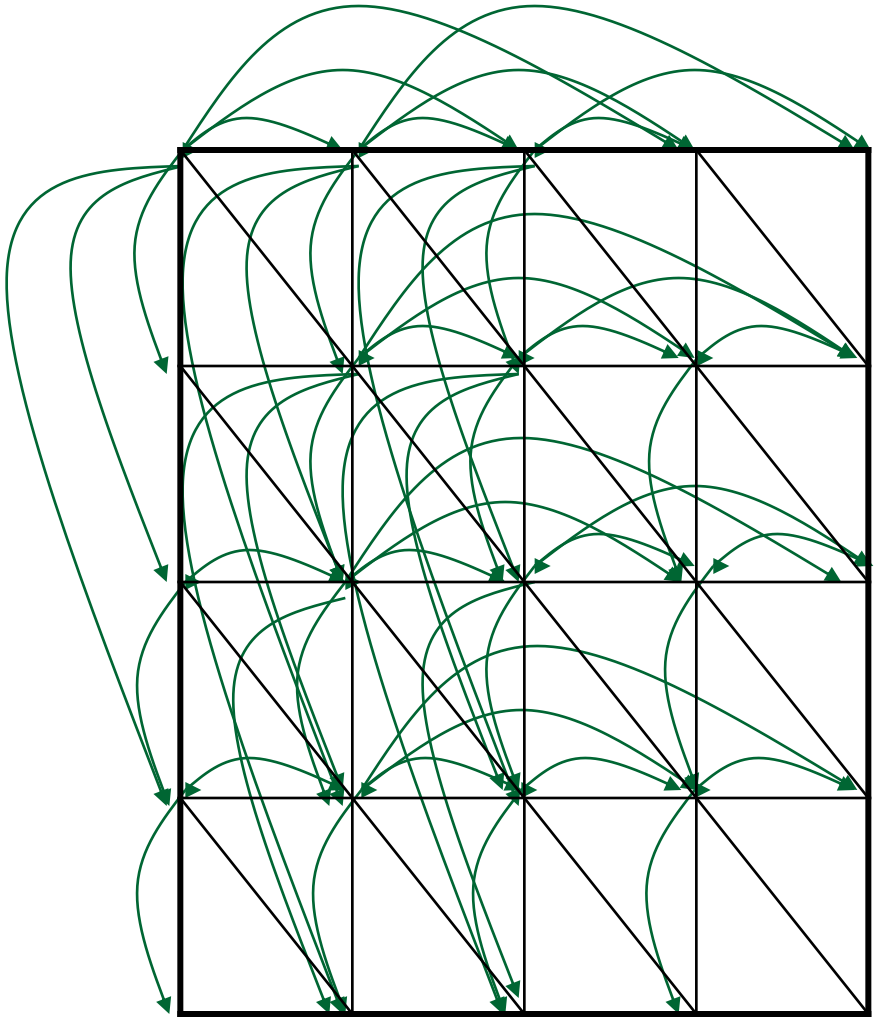
Affine Gap Penalties and Edit Graph



To reflect affine gap penalties we have to add "long" horizontal and vertical edges to the edit graph. Each such edge of length *x* should have weight

$$-\rho - x * \sigma$$

Adding "Affine Penalty" Edges to the Edit Graph



Adding them to the graph increases the running time of the alignment algorithm by a factor of ***n*** (where ***n*** is the number of vertices)

So the complexity increases from $O(n^2)$ to $O(n^3)$

We can still achieve $O(n^2)$ with dynamic programming

Affine Gap Penalty Recurrences

$$\downarrow s_{i,j} = \max \begin{cases} \downarrow s_{i-1,j} - \sigma \\ s_{i-1,j} - (\rho+\sigma) \end{cases}$$

Continue Gap in *w* (deletion)

Start Gap in *w* (deletion): from middle

$$\rightarrow s_{i,j} = \max \begin{cases} \rightarrow s_{i,j-1} - \sigma \\ s_{i,j-1} - (\rho+\sigma) \end{cases}$$

Continue Gap in *v* (insertion)

Start Gap in *v* (insertion):from middle

$$s_{i,j} = \max \begin{cases} s_{i-1,j-1} + \delta(v_i, w_j) \\ \downarrow s_{i,j} \\ \rightarrow s_{i,j} \end{cases}$$

Match or Mismatch

End deletion: from top

End insertion: from bottom

Affine Gap Penalty Recurrences (cont)

S ….. i
T ….. j

Type 1: G(i,j) is the max value of any alignment where s_i and t_j match (or mismatch)

S ….. i ------
T …… j

Type 2: E(i,j) is the max value of any alignment where t_j matches a space

S …….. i
T ….. j ------

Type 3: F(i,j) is the max value of any alignment where s_i matches a space

Affine Gap Penalty Recurrences (cont)

$$V(i,0) = F(i,0) = Wg + iWe$$

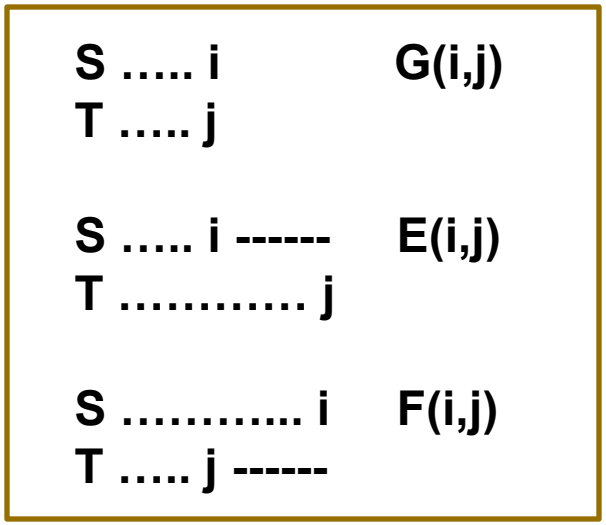
$$V(0,j) = E(0,j) = Wg + jWe$$

$$V(i,j) = \max\{G(i,j), E(i,j), F(i,j)\}$$

$$G(i,j) = V(i-1, j-1) + score(s_i, t_j)$$

$$E(i,j) = \max\begin{cases} E(i,j-1) + We, \\ G(i,j-1) + Wg + We, \\ F(i,j-1) + Wg + We \end{cases}$$

$$F(i,j) = \max\begin{cases} F(i-1,j) + We, \\ G(i-1,j) + Wg + We, \\ E(i-1,j) + Wg + We \end{cases}$$



Wg: gap opening penalty
We: gap extension penalty

LOCAL ALIGNMENT

Local vs. Global Alignment

- The Global Alignment Problem tries to find the longest path between vertices *(0,0)* and (*n,m*) in the edit graph.

- The Local Alignment Problem tries to find the longest path among paths between **arbitrary vertices** (*i,j*) and (*i', j'*) in the edit graph.

Local vs. Global Alignment

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- The Local Alignment Problem tries to find the longest path among paths between **arbitrary vertices** (*i,j*) and (*i', j'*) in the edit graph.
- In the edit graph with negatively-scored edges, Local Alignmet may score higher than Global Alignment

Local vs. Global Alignment (cont'd)

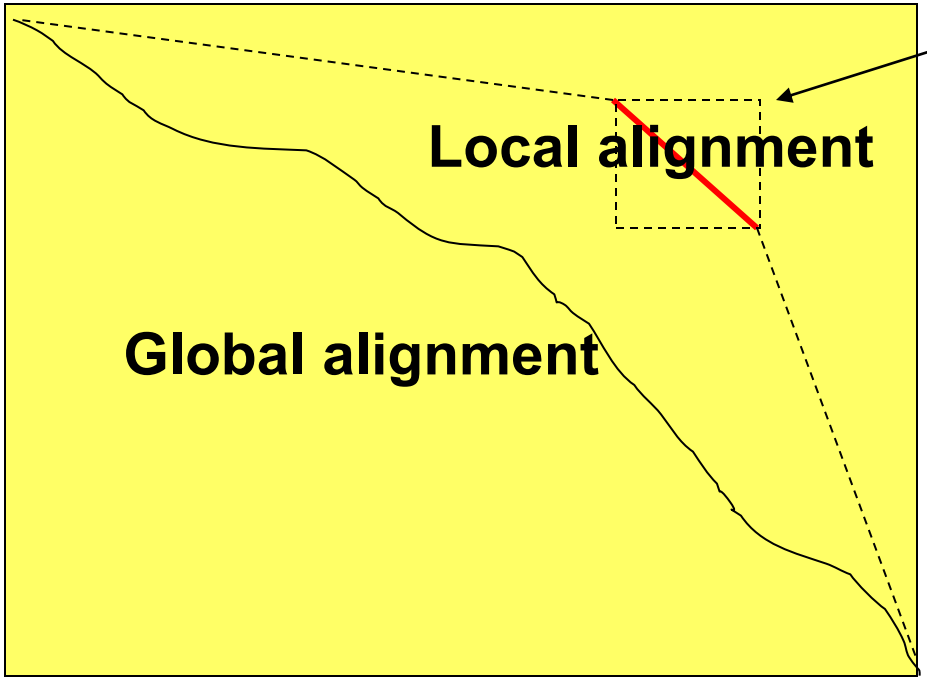
- **Global Alignment**

```
--T--CC-C-AGT--TATGT-CAGGGGACACG-A-GCATGCAGA-GAC
  |  || |  ||  | | | |||    || | | |  | ||||   |
AATTGCCGCC-GTCGT-T-TTCAG----CA-GTTATG-T-CAGAT--C
```

- **Local Alignment—better alignment to find conserved segment**

```
                    tccCAGTTATGTCAGgggacacgagcatgcagagac
                       ||||||||||||
aattgccgccgtcgttttcagCAGTTATGTCAGatc
```

Local Alignment: Example



Compute a "mini" Global Alignment to get Local

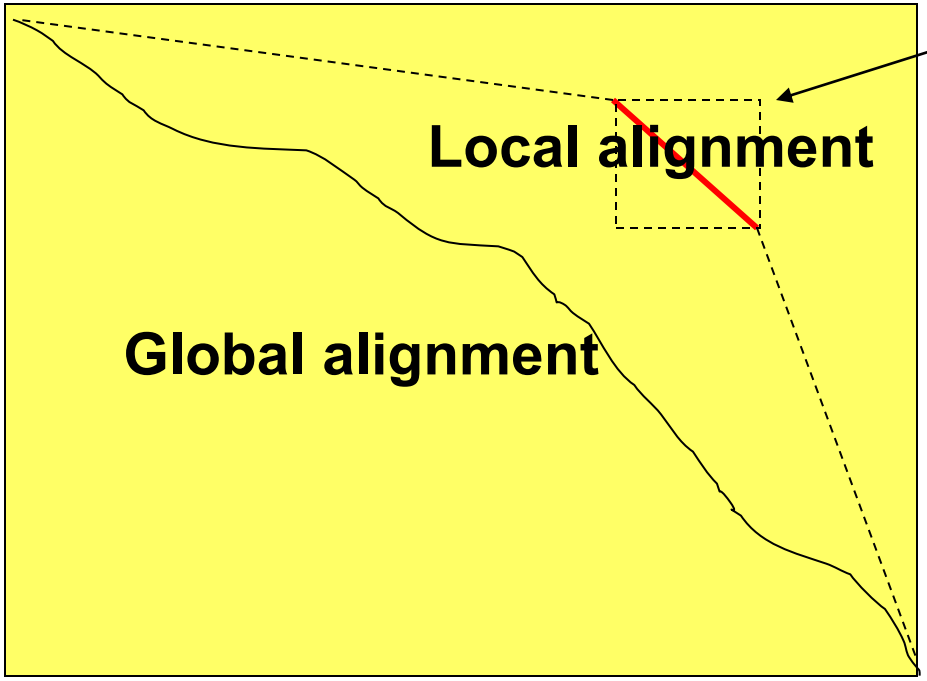
Local Alignments: Why?

- Two genes in different species may be similar over short conserved regions and dissimilar over remaining regions.
- Example:
  - Homeobox genes have a short region called the *homeodomain* that is highly conserved between species.
  - A global alignment would not find the homeodomain because it would try to align the entire sequence

The Local Alignment Problem

- Goal: Find the best local alignment between two strings
- Input : Strings **v, w** and scoring matrix δ
- Output : Alignment of substrings of **v** and **w** whose alignment score is maximum among all possible alignment of all possible substrings

Local Alignment: Example



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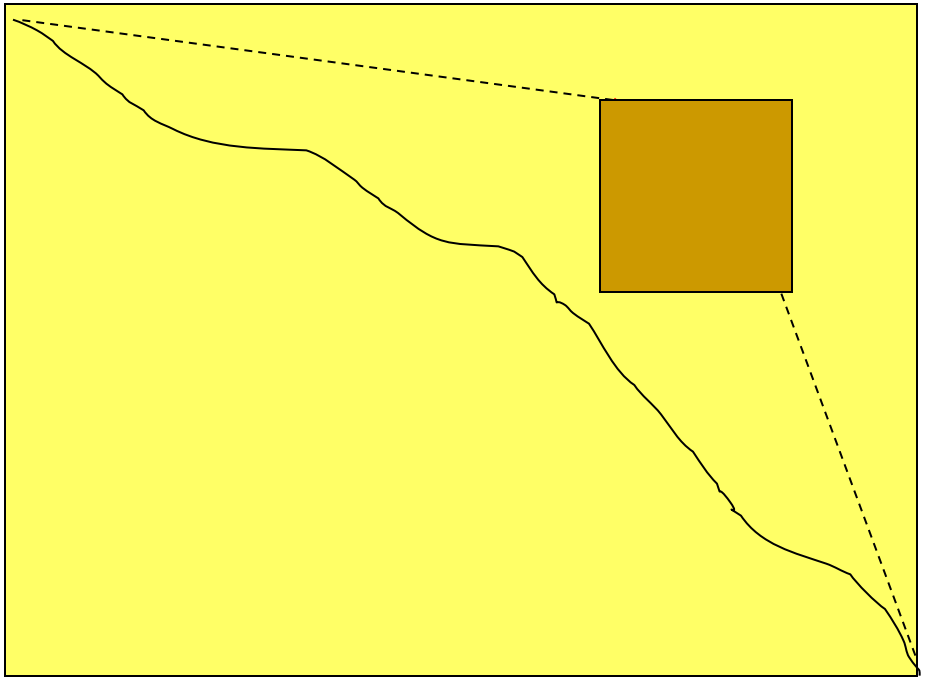
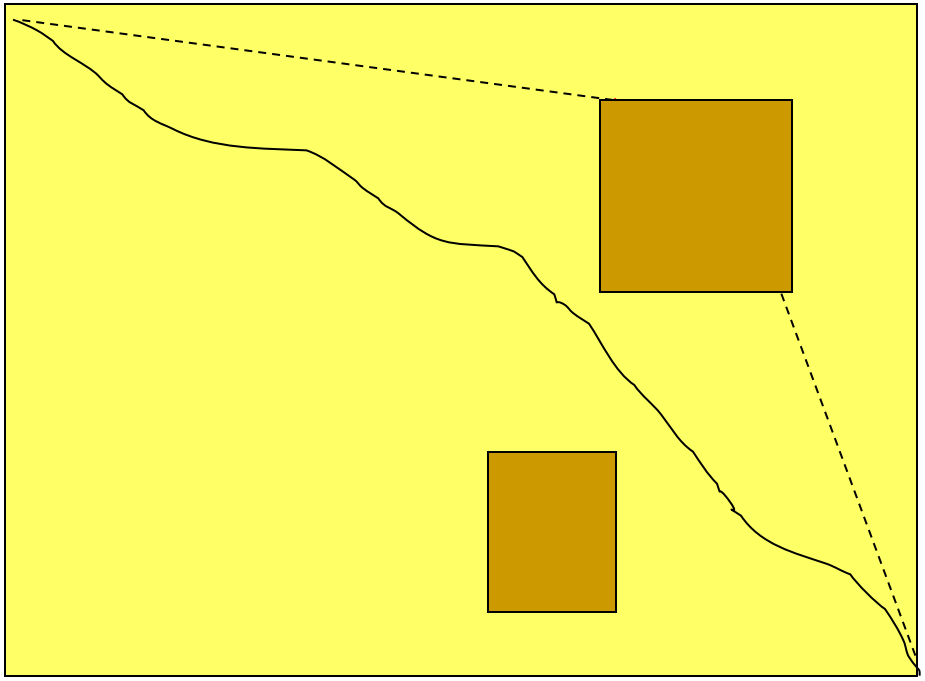
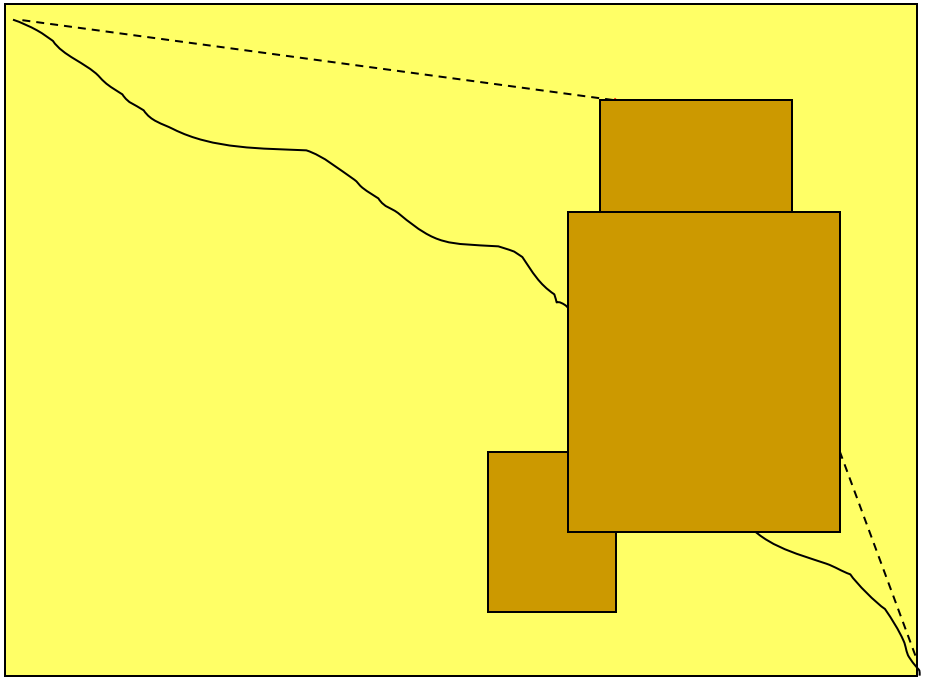
Local Alignment: Example



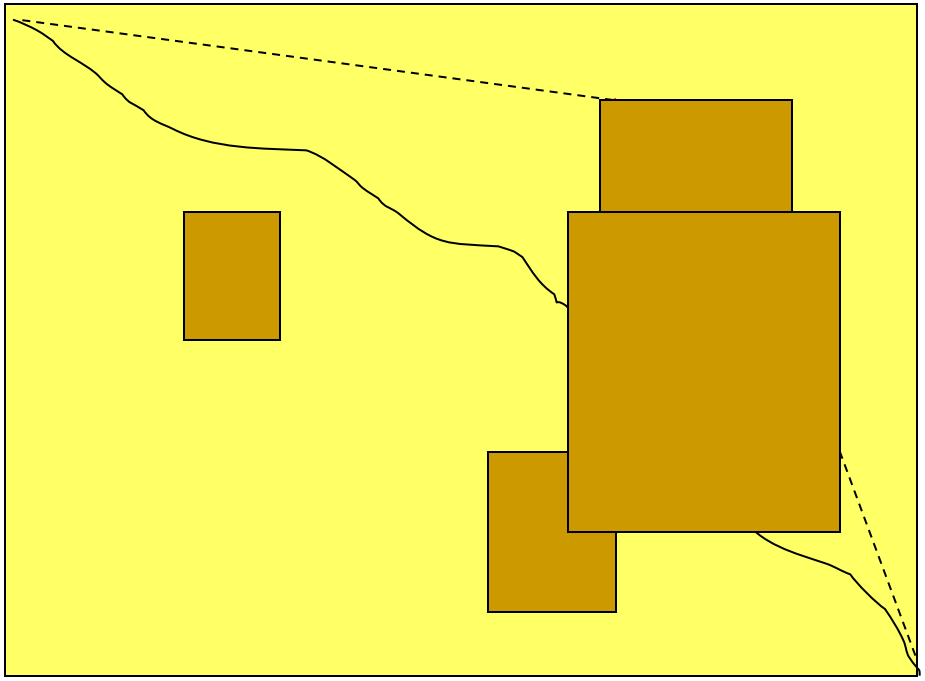
Local Alignment: Example



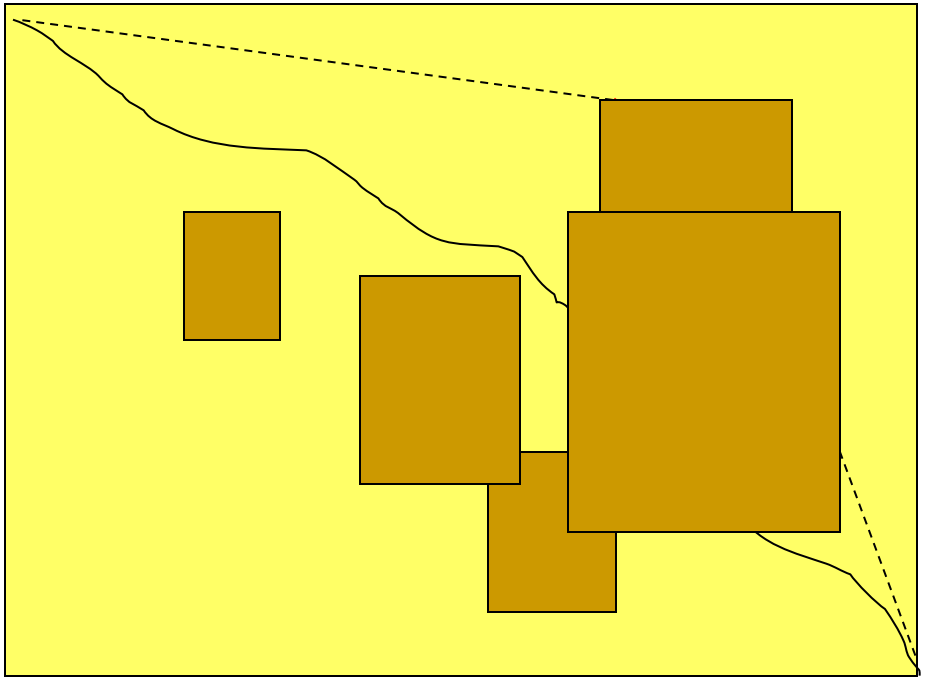
Local Alignment: Example



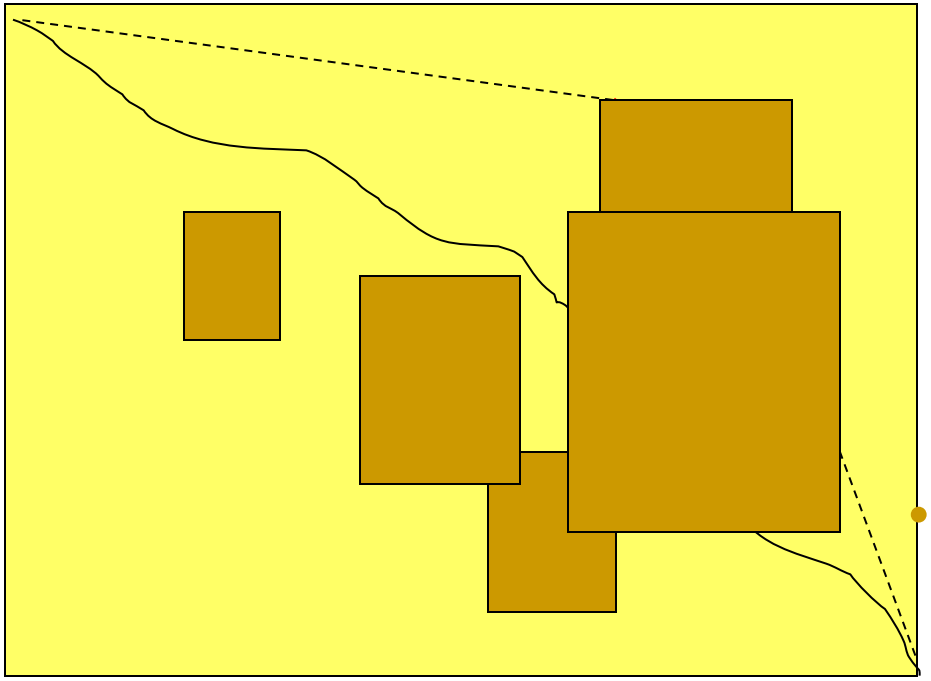
Local Alignment: Example



Local Alignment: Example



Local Alignment: Running Time



- Long run time $O(n^4)$:

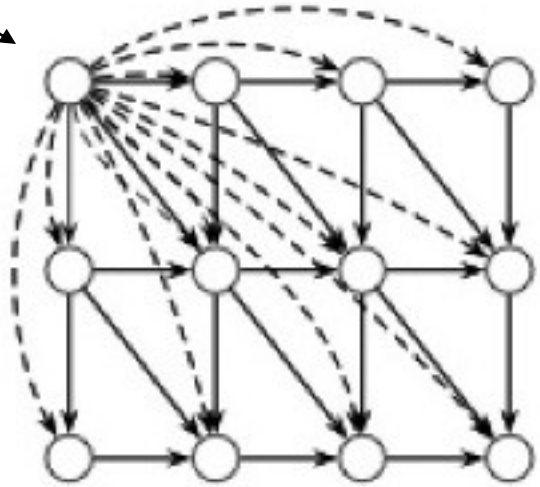
  - In the grid of size $n \times n$ there are ~n^2 vertices (i,j) that may serve as a source.

  - For each such vertex computing alignments from (i,j) to (i',j') takes $O(n^2)$ time.

- This can be remedied by giving free rides

Local Alignment: Free Rides

Vertex (0,0)



The dashed edges represent the free rides from (0,0) to every other node.

The Local Alignment Recurrence

- The largest value of $s_{i,j}$ over the whole edit graph is the score of the best local alignment.

- The recurrence:

$$s_{i,j} = max \begin{cases} 0 \\ s_{i-1,j-1} + \delta(v_i, w_j) \\ s_{i-1,j} + \delta(v_i, -) \\ s_{i,j-1} + \delta(-, w_j) \end{cases}$$

There is only this change from the original recurrence of a Global Alignment

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there is only this change from the original recurrence of a Global Alignment - since there is only one "free ride" edge entering into every vertex

Smith-Waterman: Traceback

- In the traceback, start with the cell that has the highest score and work back until a cell with a score of 0 is reached