Next

Local and global sequence 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.

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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 Alignment may score higher than Global Alignment

Local vs. Global Alignment
(cont'd)

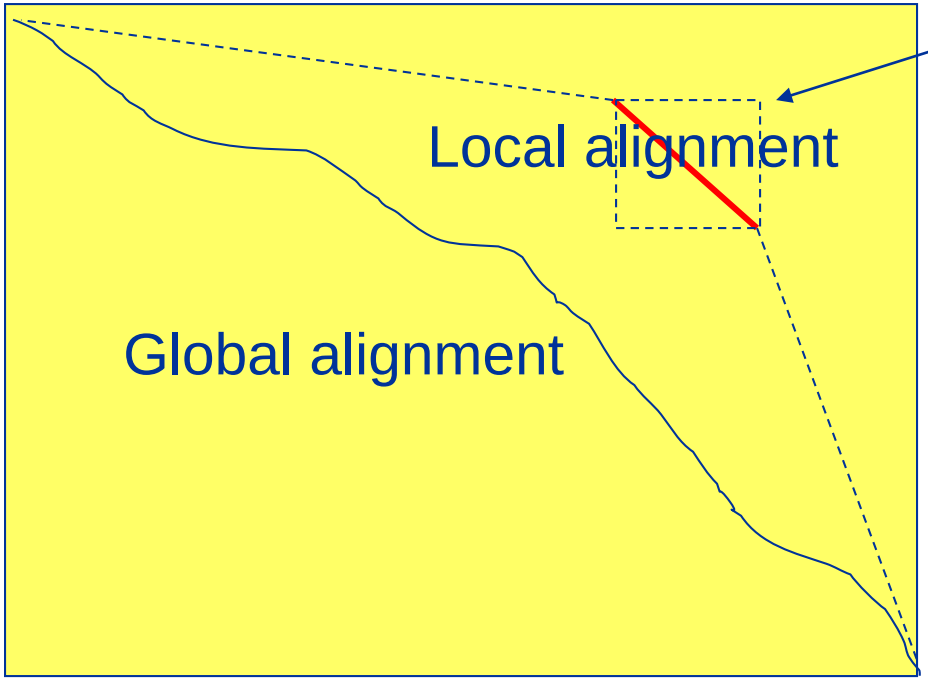
- Global Alignment

```
--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

The Problem with this Problem

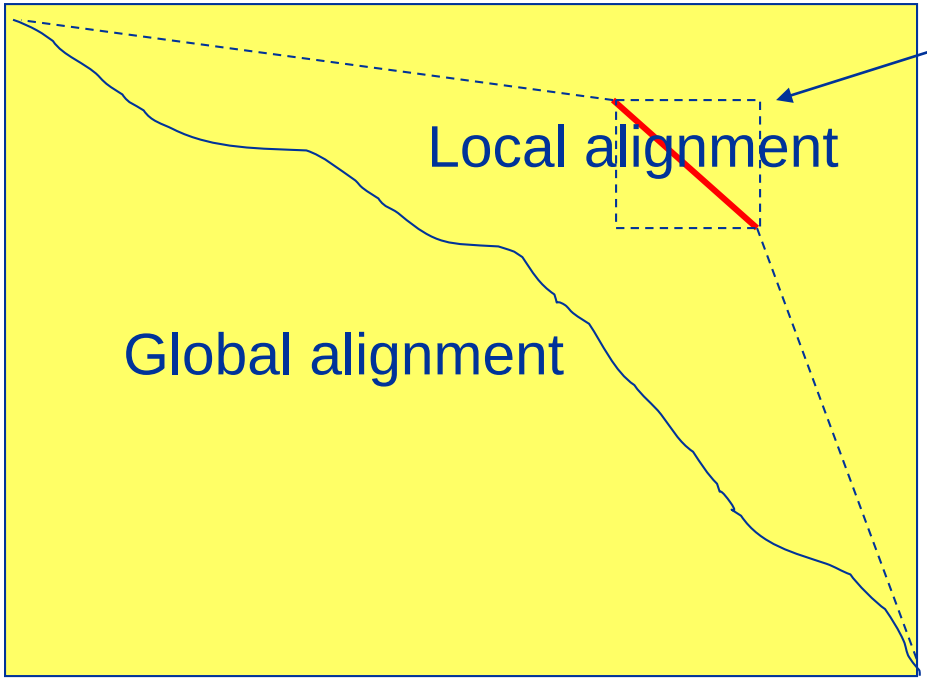
- Long run time $O(n^4)$:

  - In the grid of size *n x 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: Example



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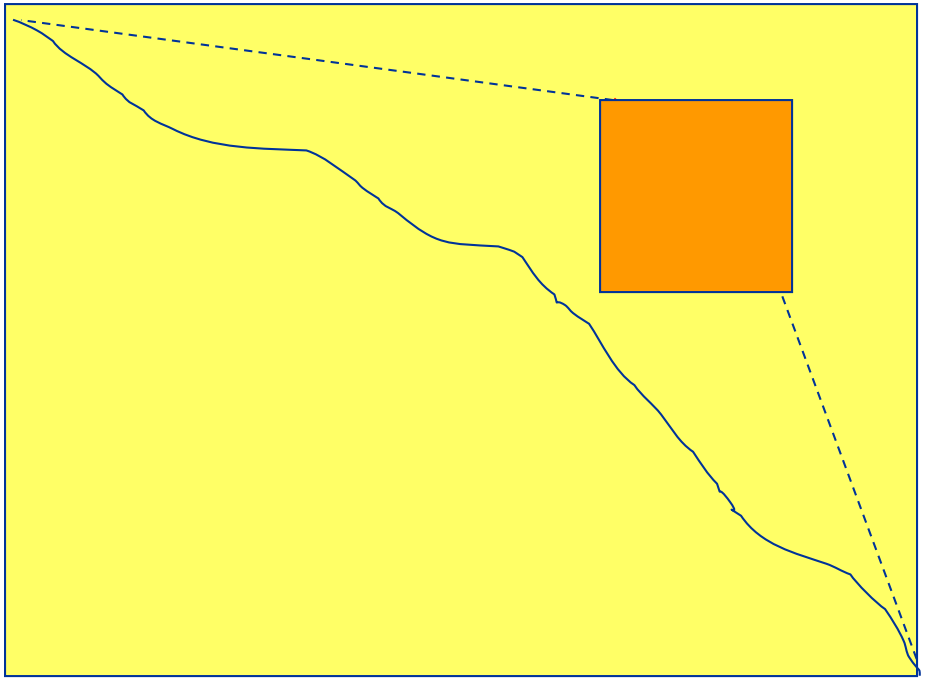

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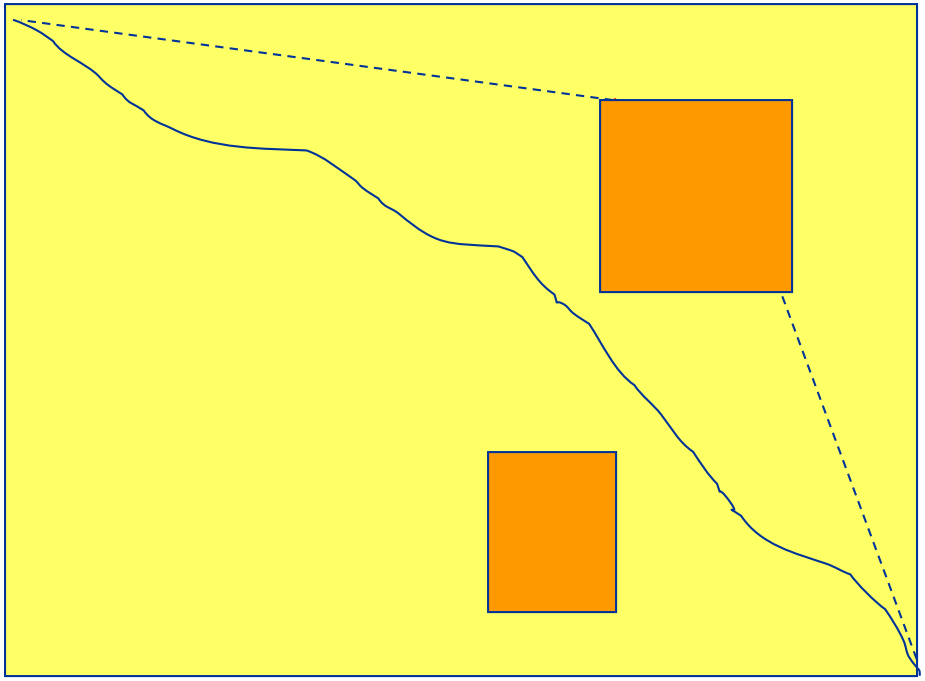

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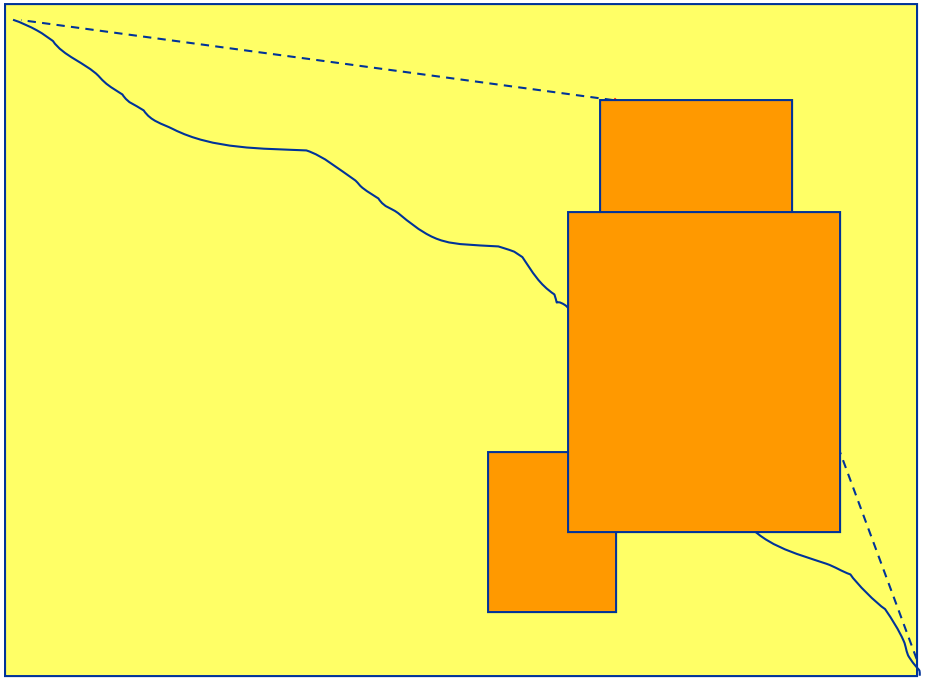

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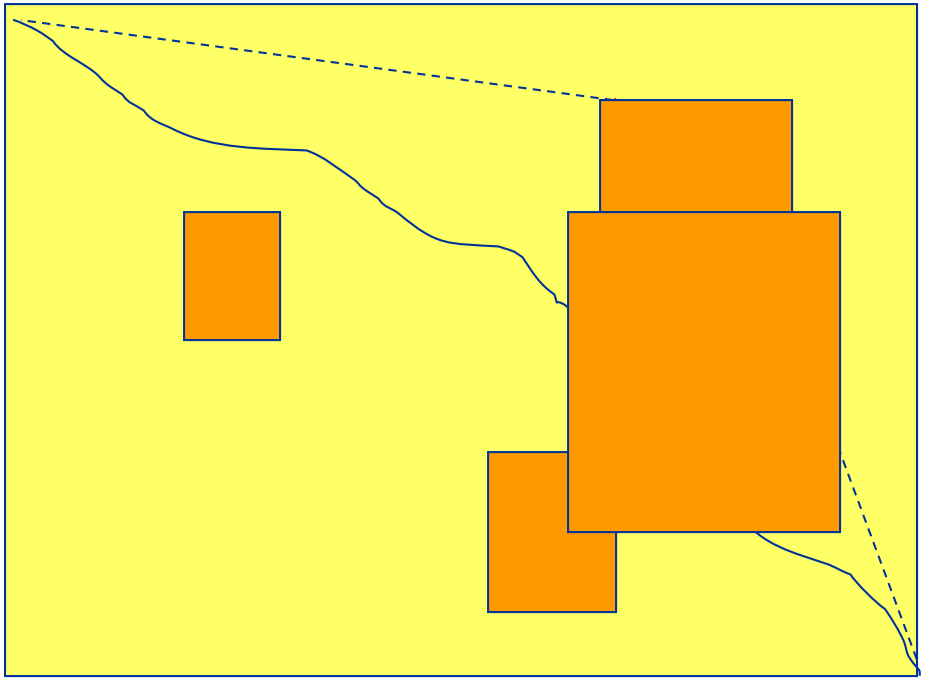

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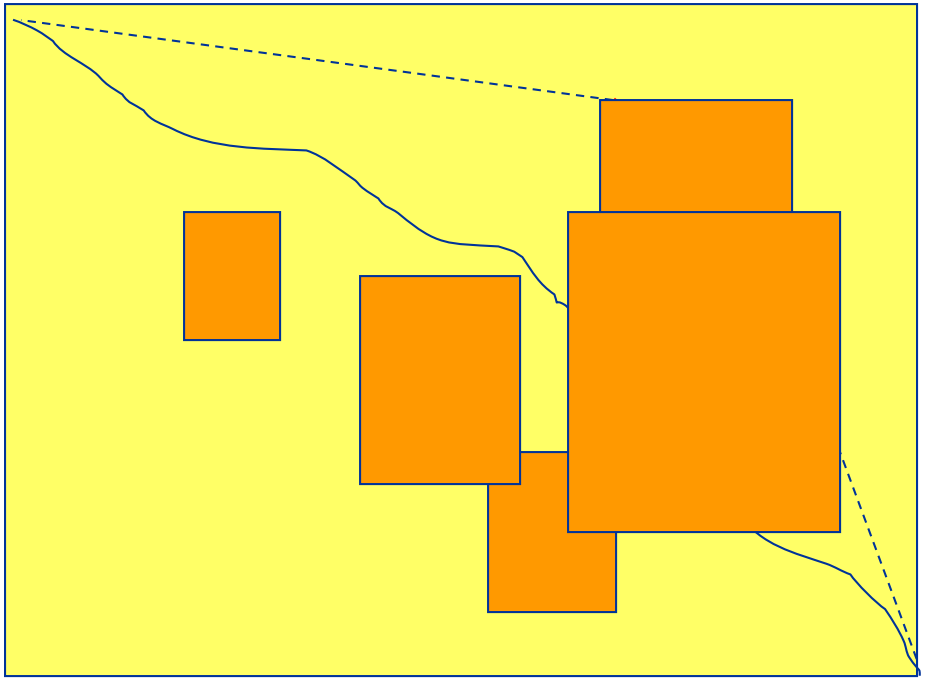
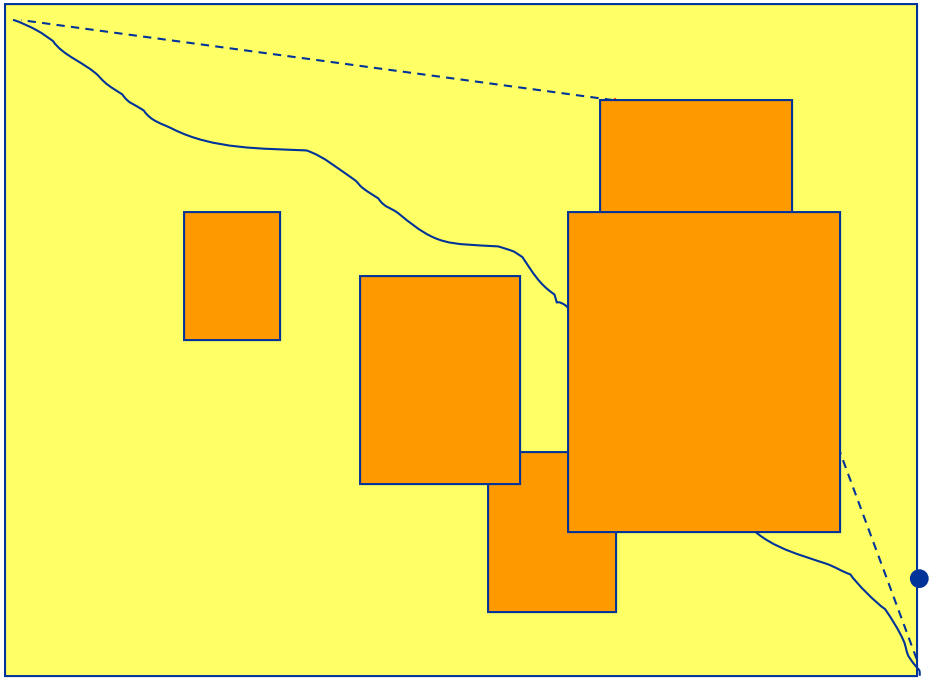


Local Alignment: Running Time



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

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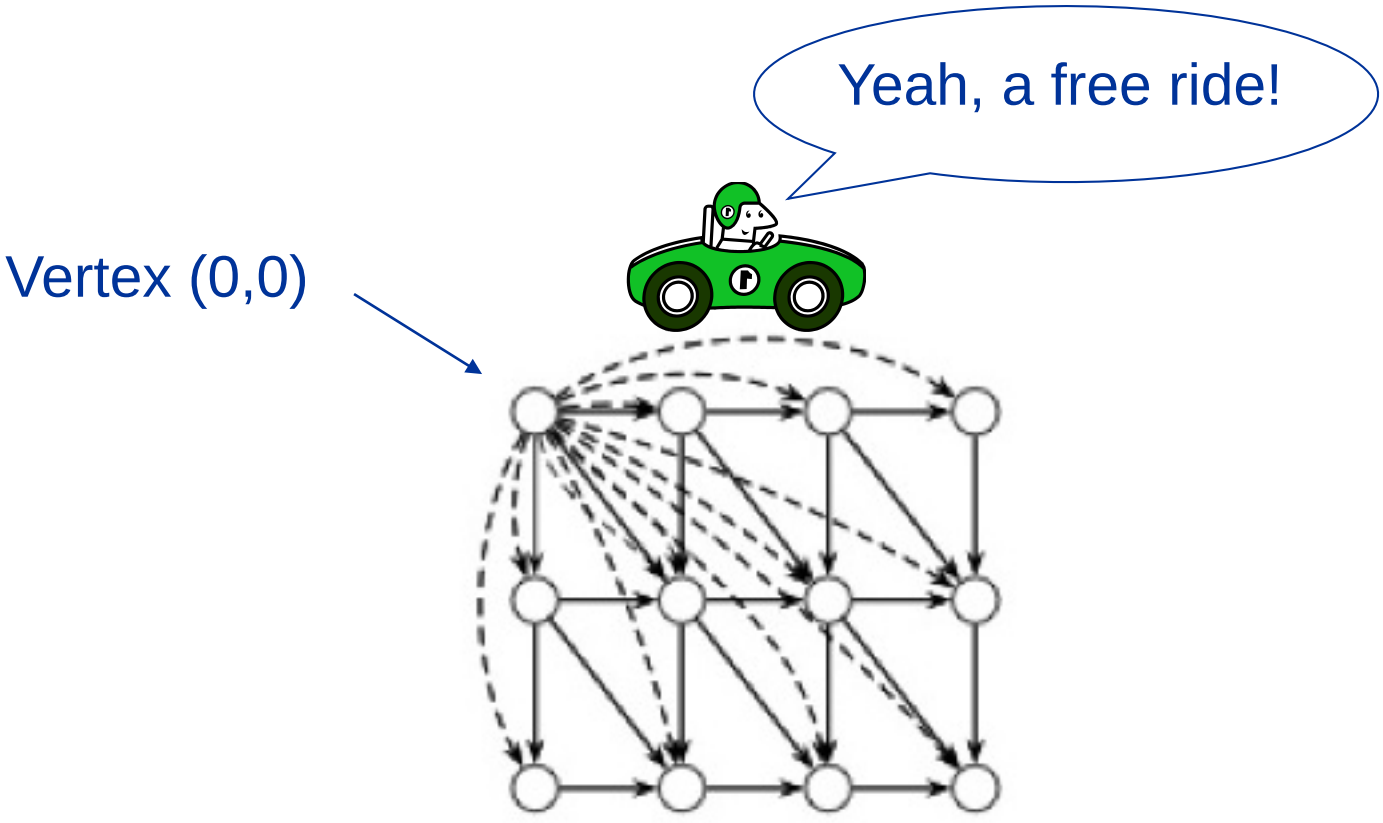
Local Alignment: Free Rides



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:

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

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

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Power of ZERO: 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

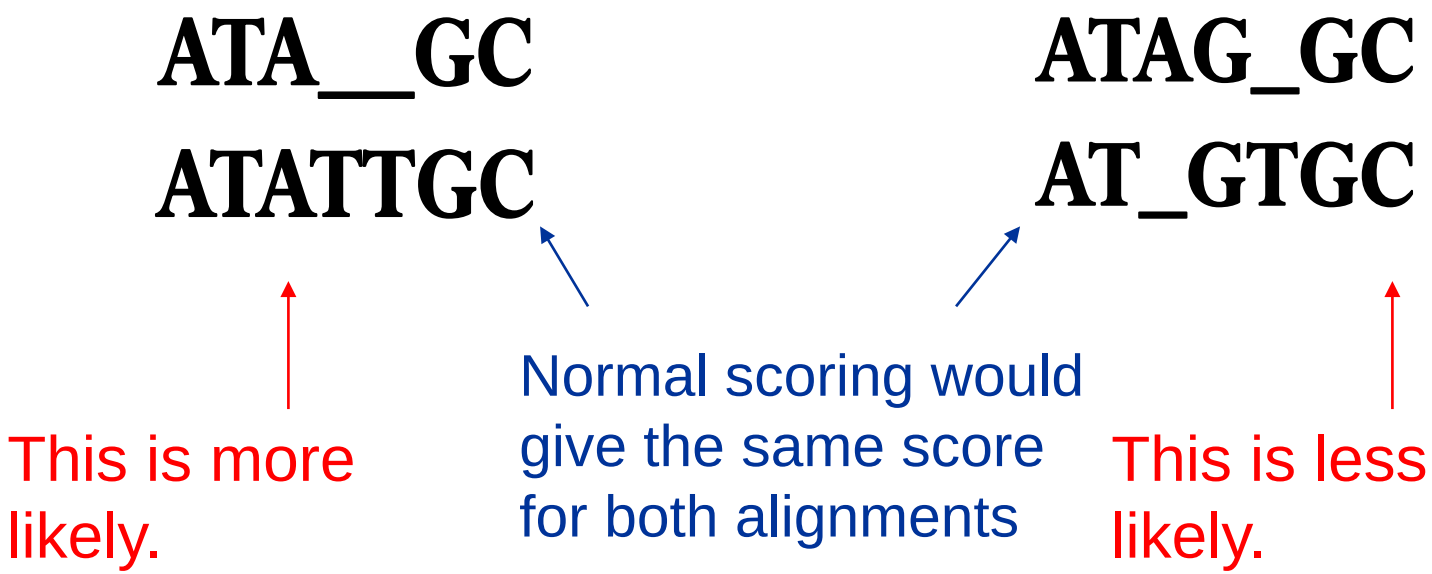
Scoring Indels: Naive Approach

- 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:

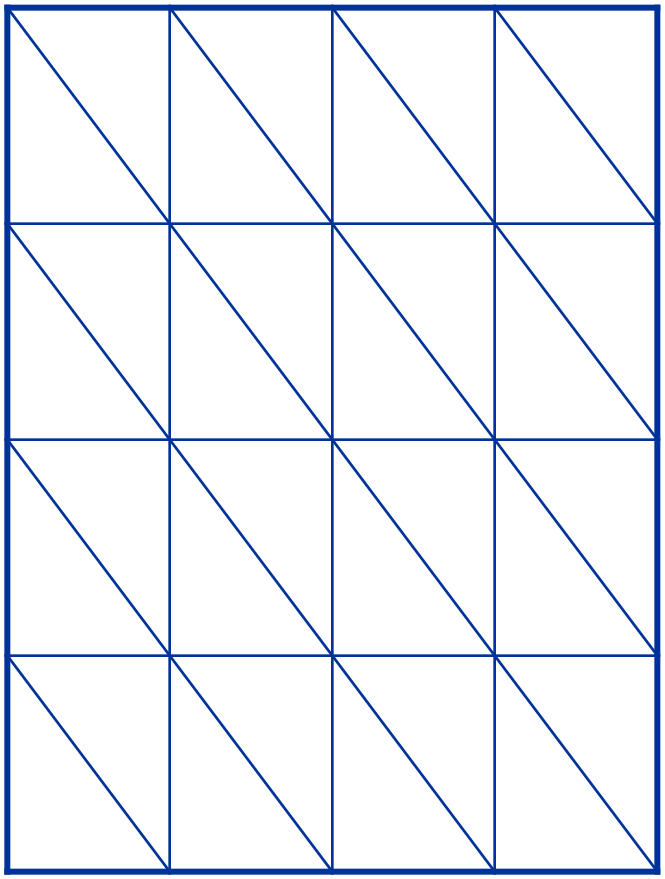
  gap extension penalty

  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

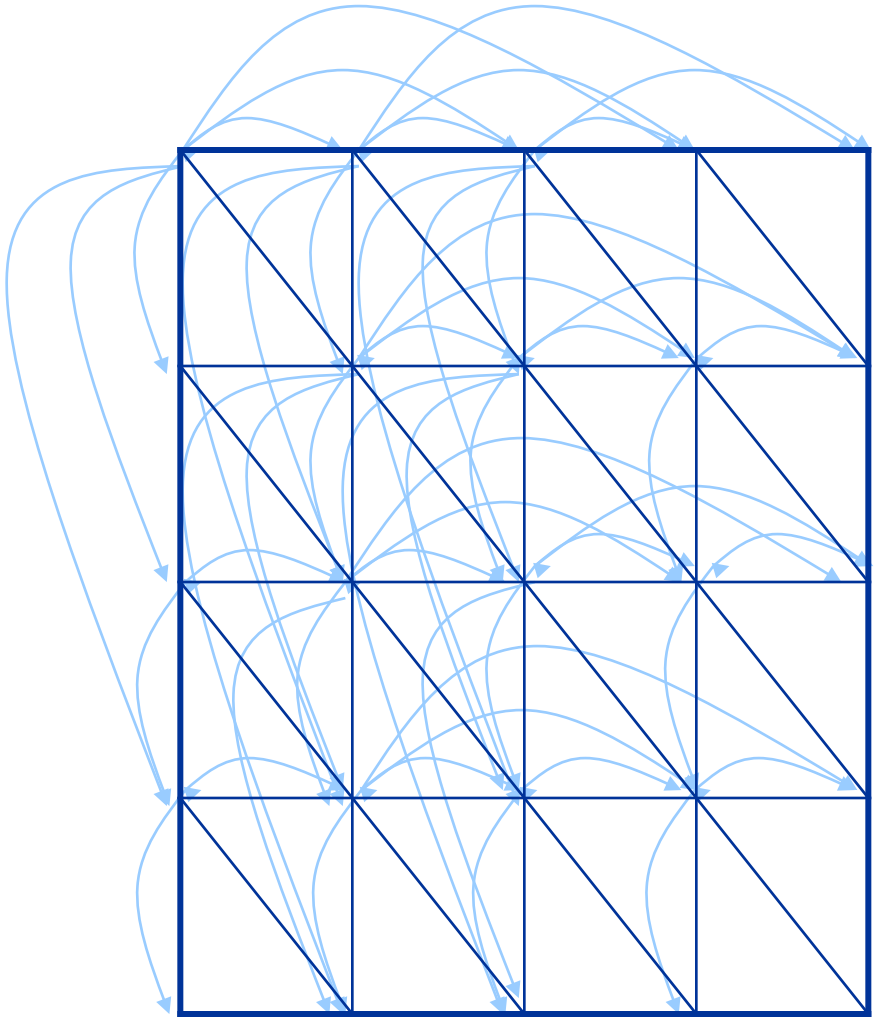
Affine Gap Penalties and Edit Graph



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

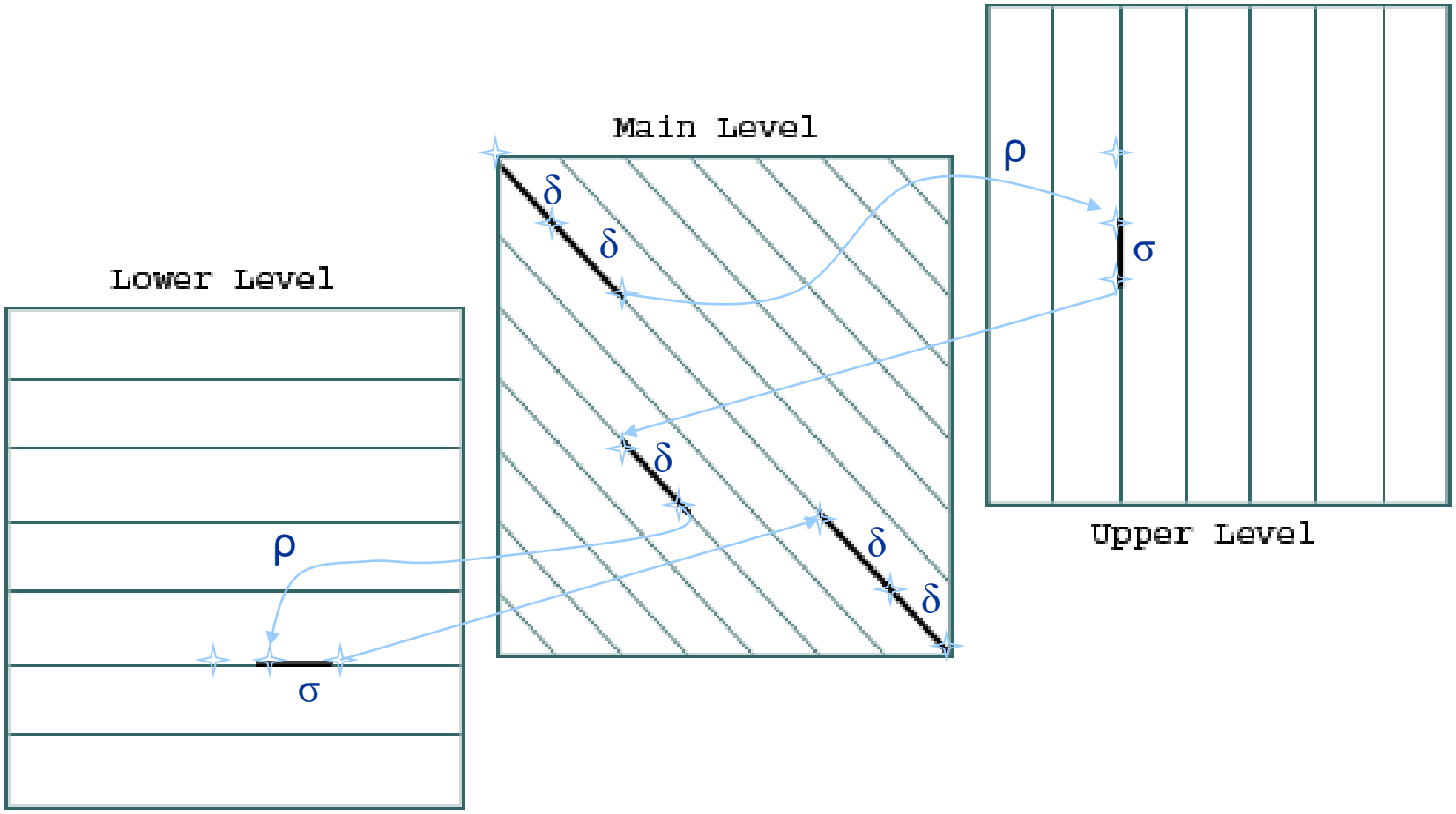


There are many such edges!

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 $O(n^3)$

Manhattan in 3 Layers



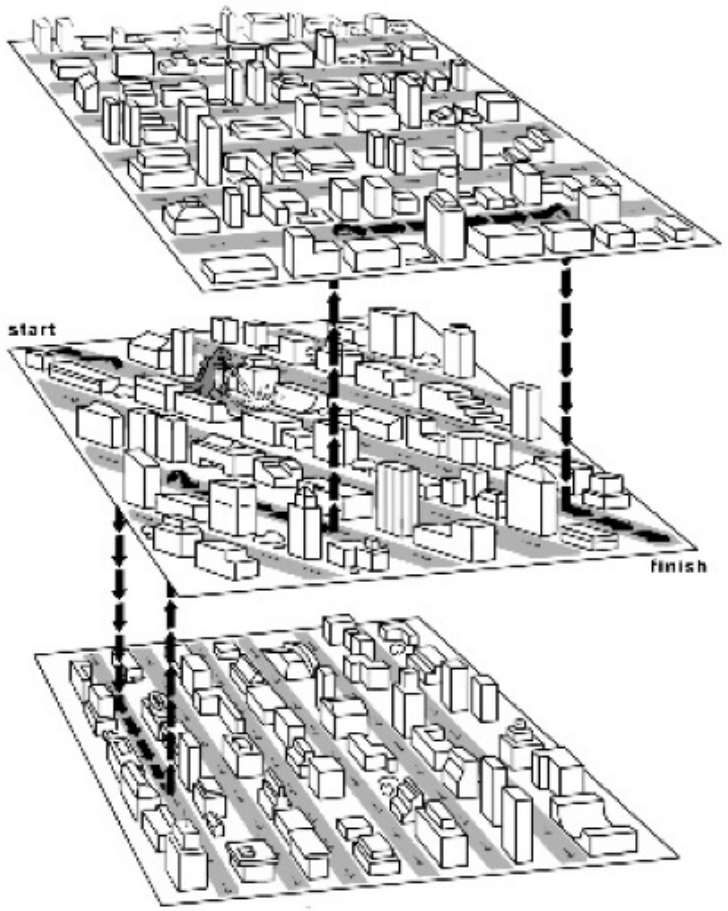
Affine Gap Penalties and 3 Layer Manhattan Grid

- The three recurrences for the scoring algorithm creates a 3-layered graph.
- The top level creates/extends gaps in the sequence *w.*
- The bottom level creates/extends gaps in sequence *v.*
- The middle level extends matches and mismatches.

Switching between 3 Layers

- Levels:
  - The **main level** is for diagonal edges
  - The **lower level** is for horizontal edges
  - The **upper level** is for vertical edges
- A jumping penalty is assigned to moving from the main level to either the upper level or the lower level ($-\rho-\sigma$)
- There is a gap extension penalty for each continuation on a level other than the main level ($-\sigma$)

The 3-leveled Manhattan Grid



Gaps in w

Matches/Mismatches

Gaps in v

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

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

Match or Mismatch

End deletion: from top

End insertion: from bottom