Gap Penalties

CMSC 423

General Gap Penalties

```
AAAGAATTCA                 AAAGAATTCA
                  vs.
A-A-A-T-CA                 AAA----TCA
```

These have the same score, but the second one is often more plausible.

A single insertion of “GAAT” into the first string could change it into the second.

- Now, the cost of a run of k gaps is $gap \times k$
- It might be more realistic to support general gap penalty, so that the score of a run of k gaps is $\mathbf{gap}(k) < gap \times k$.
- Then, the optimization will prefer to group gaps together.

General Gap Penalties

```
AAAGAATTCA          AAAGAATTCA
A-A-A-T-CA    vs.   AAA----TCA
```

Previous DP no longer works with general gap penalties because the score of the last character depends on details of the previous alignment:

```
AAAGAAC          AAAGAATC
AAA----    vs.   AAA-----
```

Instead, we need to "know" how long a final run of gaps is in order to give a score to the last subproblem.

Three Matrices

We now keep 3 different matrices:

M[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a character-character **match or mismatch**.

X[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in X**.

Y[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in Y**.

$$M[i,j] = \mathrm{match}(i,j) + \max \begin{cases} M[i-1,j-1] \\ X[i-1,j-1] \\ Y[i-1,j-1] \end{cases}$$

$$X[i,j] = \max \begin{cases} M[i,j-k] - \mathrm{gap}(k) & \text{for } 1 \leq k \leq j \\ Y[i,j-k] - \mathrm{gap}(k) & \text{for } 1 \leq k \leq j \end{cases}$$

$$Y[i,j] = \max \begin{cases} M[i-k,j] - \mathrm{gap}(k) & \text{for } 1 \leq k \leq i \\ X[i-k,j] - \mathrm{gap}(k) & \text{for } 1 \leq k \leq i \end{cases}$$

The M Matrix

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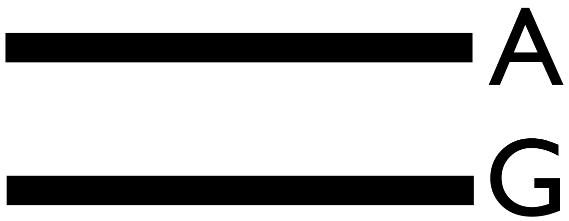
X[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in X**.

Y[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in Y**.

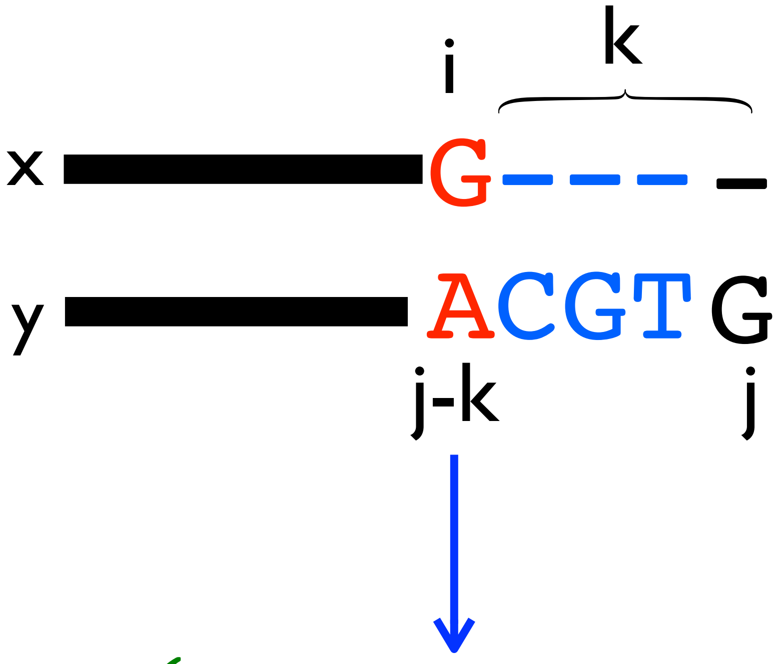
By definition, alignment ends in a match.

$$M[i,j] = \text{match}(i,j) + \max \begin{cases} M[i-1,j-1] \\ X[i-1,j-1] \\ Y[i-1,j-1] \end{cases}$$

Any kind of alignment is allowed before the match.



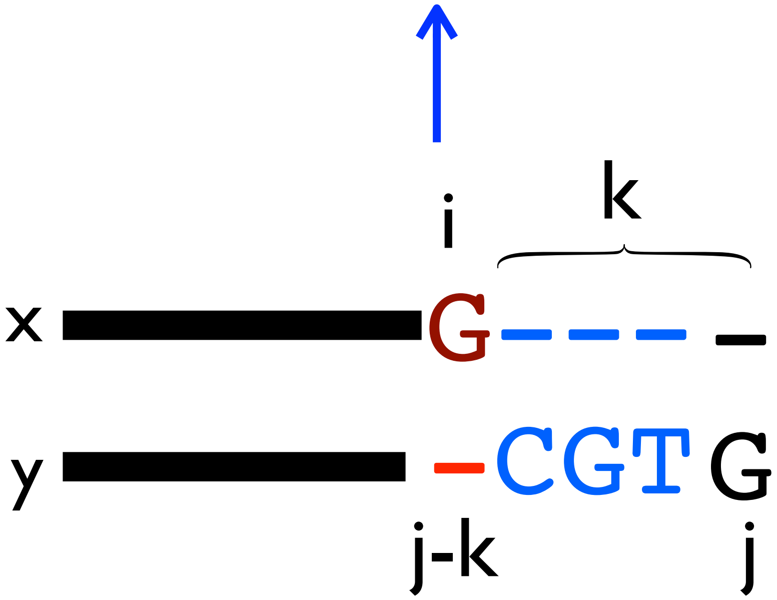
The X (and Y) matrices



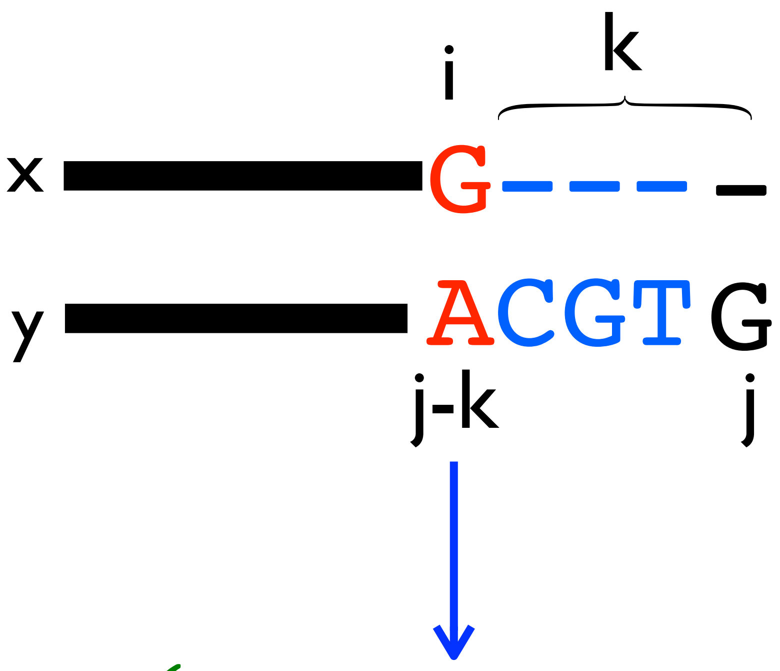
k decides how long to make the gap.

We have to make the whole gap at once in order to know how to score it.

$$X[i,j] = \max\begin{cases} M[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \\ Y[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \end{cases}$$



The X (and Y) matrices



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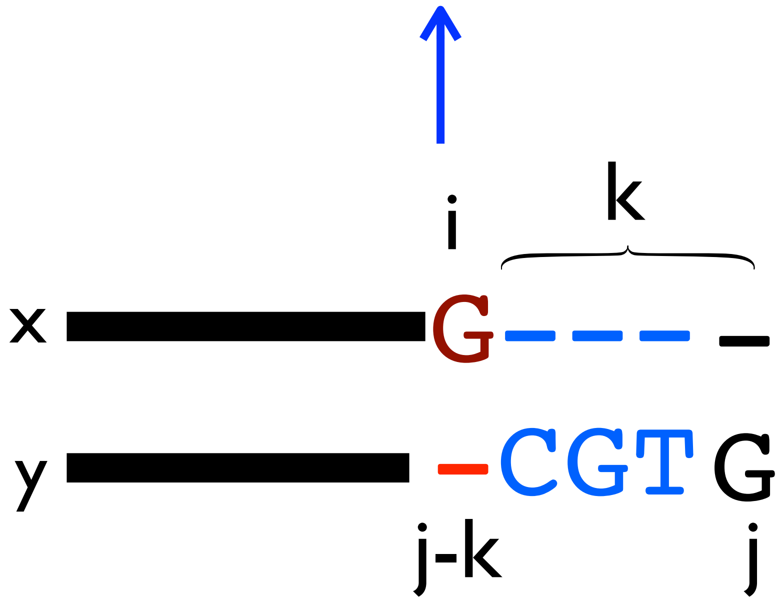
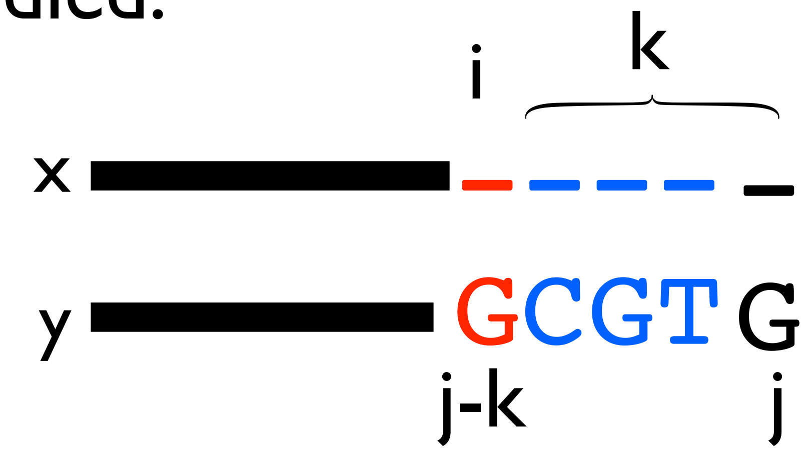
$$X[i,j] = \max\begin{cases} M[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \\ Y[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \end{cases}$$



This case is automatically handled.



Running Time for Gap Penalties

$$M[i,j] = \text{match}(i,j) + \max \begin{cases} M[i-1,j-1] \\ X[i-1,j-1] \\ Y[i-1,j-1] \end{cases}$$

$$X[i,j] = \max \begin{cases} M[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \\ Y[i,j-k] - \text{gap}(k) & \text{for } 1 \le k \le j \end{cases}$$

$$Y[i,j] = \max \begin{cases} M[i-k,j] - \text{gap}(k) & \text{for } 1 \le k \le i \\ X[i-k,j] - \text{gap}(k) & \text{for } 1 \le k \le i \end{cases}$$

Final score is max {M[n,m], X[n,m], Y[n,m]}.

How do you do the traceback?

Runtime:

- Assume |X| = |Y| = n for simplicity: $3n^2$ subproblems
- $2n^2$ subproblems take O(n) time to solve (because we have to try all k)

⇒ $O(n^3)$ total time

Affine Gap Penalties

- $O(n^3)$ for general gap penalties is usually too slow...
- We can still encourage spaces to group together using a special case of general penalties called *affine gap penalties*:

  gap_start = the cost of starting a gap

  gap_extend = the cost of extending a gap by one more space
- Same idea of using 3 matrices, but now we don't need to search over all gap lengths, we just have to know whether we are starting a new gap or not.

Affine Gap Penalties

$$M[i,j] = \text{match}(i,j) + \max \begin{cases} M[i-1,j-1] \\ X[i-1,j-1] \\ Y[i-1,j-1] \end{cases}$$

match between x and y

If previous alignment ends in match, this is a new gap

$$X[i,j] = \max \begin{cases} \text{gap\_start} + \text{gap\_extend} + M[i,j-1] \\ \text{gap\_extend} + X[i,j-1] \\ \text{gap\_start} + \text{gap\_extend} + Y[i,j-1] \end{cases}$$

gap in x

$$Y[i,j] = \max \begin{cases} \text{gap\_start} + \text{gap\_extend} + M[i-1,j] \\ \text{gap\_start} + \text{gap\_extend} + X[i-1,j] \\ \text{gap\_extend} + Y[i-1,j] \end{cases}$$

gap in y

Affine Base Cases

- M[0, i] = "score of best alignment between 0 characters of x and i characters of y that ends in a match" = $-\infty$ because no such alignment can exist.

- X[0, i] = "score of best alignment between 0 characters of x and i characters of y that ends in a gap in x" = gap_start + i × gap_extend because this alignment looks like:

```
---------
yyyyyyyyy
```

- X[i, 0] = "score of best alignment between i characters of x and 0 characters of y that ends in a gap in X" = $-\infty$

```
xxxxxxxxx-
----------
```

← not allowed

- M[i, 0] = M[0, i] and Y[0, i] and Y[i,0] are computed using the same logic as X[i,0] and X[0,i]

Affine Gap Runtime

- $3n^2$ subproblems
- Each one takes constant time
- Total runtime $O(n^2)$, back to the run time of the basic running time.

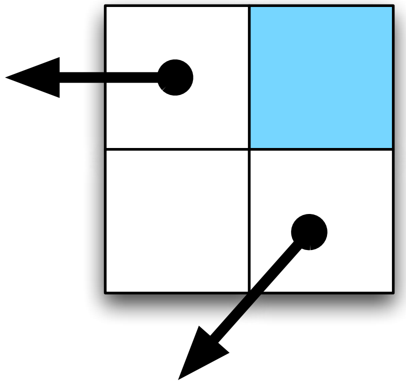
Why do you "need" 3 matrices?

- Alternative WRONG algorithm:

```
M[i][j] = max(
    M[i-1][j-1] + cost(x[i], y[i]),
    M[i-1][j] + gap + (gap_start if Arrow[i-1][j] != ← ),
    M[j][i-1] + gap + (gap_start if Arrow[i][j-1] !=  ↓ )
)
```

WRONG Intuition: we only need to know whether we are starting a gap or extending a gap.

The arrows coming out of each subproblem tell us how the best alignment ends, so we can use them to decide if we are starting a new gap.



The best alignment up to this cell ends in a gap.

The best alignment up to this cell ends in a match.

PROBLEM: The best alignment for strings x[1..i] and y[1..j] doesn't have to be used in the best alignment between x[1..i+1] and y[1..j+1]

Why 3 Matrices: Example

match = 10, mismatch = -2, gap = -7, gap_start = -15

```
CART
CA-T
```

$$\text{OPT}(4, 3) = \text{optimal score} = \underbrace{30 - 15 - 7} = 8$$

```
CARTS
CA-T-
```

$$\text{WRONG}(5, 3) = \overbrace{30 - 15 - 7} - 15 - 7 = -14$$

```
CARTS
CAT--
```

$$\text{OPT}(5, 3) = 20 - 2 - 15 - 14 = -11$$

this is why we need to keep the X and Y matrices around.
they tell us the score of ending with a gap in one of the sequences.

Side Note: Lower Bounds

- Suppose the lengths of x and y are n.
- Clearly, need at least $\Omega(n)$ time to find their global alignment (have to read the strings!)
- The DP algorithms show global alignment can be done in $O(n^2)$ time.
- A trick called the "Four Russians Speedup" can make a similar dynamic programming algorithm run in $O(n^2 / \log n)$ time.
  - We probably won't talk about the Four Russian's Speedup.
- Open questions: Can we do better? Can we prove that we can't do better? No one knows...

Recap

- Local alignment: extra “0” case.

- General gap penalties require 3 matrices and $O(n^3)$ time.
- Affine gap penalties require 3 matrices, but only $O(n^2)$ time.

What you should know by now...

- Dynamic programming framework
- Global & local sequence alignment algorithms with basic gap penalties
- Alignment with general gap penalties
- Alignment with affine gap penalties
- Longest common subsequence
- Subset Sum