Sequence comparison: Dynamic programming

Genome 559: Introduction to Statistical and Computational Genomics

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Sequence comparison overview

- Problem: Find the "best" alignment between a query sequence and a target sequence.
- To solve this problem, we need
  - a method for scoring alignments, and
  - an algorithm for finding the alignment with the best score.
- The alignment score is calculated using
  - a substitution matrix
  - gap penalties.
- The algorithm for finding the best alignment is dynamic programming (DP).

A simple alignment problem.

- Problem: find the best pairwise alignment of `GAATC` and `CATAC`.
- Use a linear gap penalty of -4.
- Use the following substitution matrix:

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

How many possibilities?

```
GAATC      GAAT-C     -GAAT-C
CATAC      C-ATAC     C-A-TAC

GAATC-     GAAT-C     GA-ATC
CA-TAC     CA-TAC     CATA-C
```

- How many different possible alignments of two sequences of length n exist?

How many possibilities?

```
GAATC      GAAT-C     -GAAT-C
CATAC      C-ATAC     C-A-TAC

GAATC-     GAAT-C     GA-ATC
CA-TAC     CA-TAC     CATA-C
```

- How many different alignments of two sequences of length ***n*** exist?

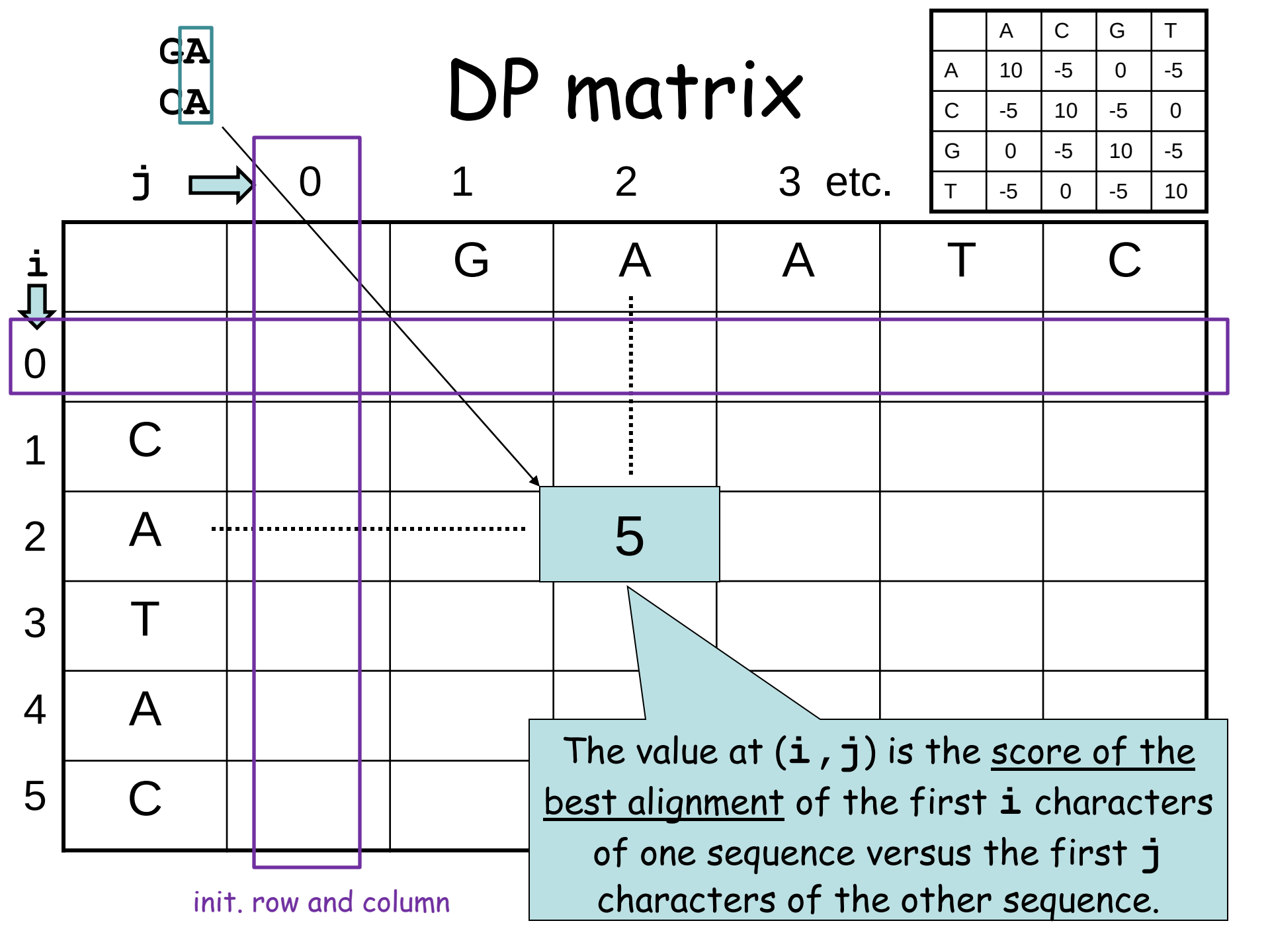
5	2.5×10^2
10	1.8×10^5
20	1.4×10^{11}
30	1.2×10^{17}
40	1.1×10^{23}

$$\binom{2n}{n} = \frac{(2n)!}{(n!)^2}$$

2n choose n - the binomial coefficient

FYI for two sequences of length m and n, possible alignments number:

$$\binom{mn}{\min(m,n)} = \frac{(mn)!}{(\min(m,n)!)^2}$$



	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

GAA
CA–

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
C						
A			5	1		
T						
A						
C						

Moving horizontally in the matrix introduces a gap in the sequence along the left edge.

GA-
CAT

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
C						
A			5			
T			1			
A						
C						

Moving vertically in the matrix introduces a gap in the sequence along the top edge.

GAA
CAT

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
C						
A			5			
T				0		
A						
C						

Moving diagonally in the matrix aligns two residues

Start at top left and move progressively

Initialization

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0					
C						
A						
T						
A						
C						

G
–

Introducing a gap

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4				
C						
A						
T						
A						
C						

Introducing a gap

–
C

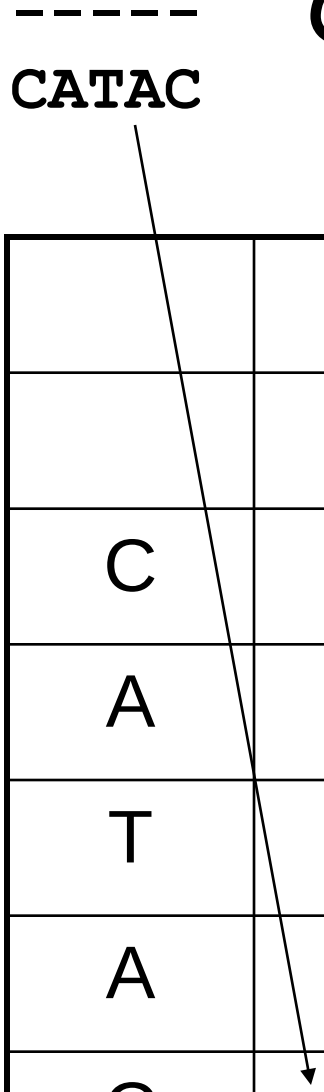
	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4				
C	-4					
A						
T						
A						
C						

Complete first row and column

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4					
A	-8					
T	-12					
A	-16					
C	-20					



Three ways to get to i=1, j=1

G-
-C

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

j ⇨ 0 1 2 3 etc.

i ⇩

		G	A	A	T	C
0	0 →	-4 ↓				
1 C		-8				
2 A						
3 T						
4 A						
5 C						

Three ways to get to i=1, j=1

-G
C-

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

j ⇨ 0 1 2 3 etc.

i ⇩			G	A	A	T	C
0		0					
1	C	-4 →	-8				
2	A						
3	T						
4	A						
5	C						

G
C

Three ways to get to i=1, j=1

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

j ⇨ 0 1 2 3 etc.

i ⇩

		G	A	A	T	C
0	0					
1 C		-5				
2 A						
3 T						
4 A						
5 C						

Accept the highest scoring of the three

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↘	-5				
A	-8					
T	-12					
A	-16					
C	-20					

Then simply repeat the same rule progressively across the matrix

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↘	-5				
A	-8	?				
T	-12					
A	-16					
C	-20					

-G
CA
-4

~~G-~~
~~CA~~
-9

~~--G~~
~~CA-~~
-12

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4	-5				
A	-8	?				
T	-12					
A	-16					
C	-20					

0

~~-4~~

-4

~~→~~

-G
CA
-4

~~G-~~
~~CA~~
-9

~~--G~~
~~CA-~~
-12

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4	-5				
A	-8	-4				
T	-12					
A	-16					
C	-20					

0 -4 -4

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↓ ↘	-5				
A	-8 ↓ ↘	-4				
T	-12 ↓	?				
A	-16 ↓	?				
C	-20	?				

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↓	-5				
A	-8 ↓	-4 ↓				
T	-12 ↓	**-8** ↓				
A	-16 ↓	**-12** ↓				
C	-20	**-16**				

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↓ ↘	-5	?			
A	-8 ↓ ↘	-4 ↓	?			
T	-12 ↓ ↘	-8 ↓	?			
A	-16 ↓	-12 ↓	?			
C	-20	-16	?			

Traceback

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↓	-5 ↓	**-9**			
A	-8 ↓	-4 ↓	**5** ↓			
T	-12 ↓	-8 ↓	**1** ↓			
A	-16 ↓	-12 ↓	**2** ↓			
C	-20	-16	**-2**			

What is the alignment associated with this entry?

(just follow the arrows back - this is called the traceback)

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0 →	-4 →	-8 →	-12 →	-16 →	-20
C	-4 ↓	-5 →	**-9**			
A	-8 ↓	-4 ↓	**5** ↓			
T	-12 ↓	-8 ↓	**1** ↓			
A	-16 ↓	-12 ↓	**2** ↓			
C	-20	-16	**-2**			

-G-A
CATA

DP matrix

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0	-4	-8	-12	-16	-20
C	-4	-5	-9			
A	-8	-4	5			
T	-12	-8	1			
A	-16	-12	2			
C	-20	-16	-2			?

Continue and find the optimal global alignment, and its score.

Best alignment starts at bottom right and follows traceback arrows to top left

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0	-4	-8	-12	-16	-20
C	-4	-5	-9	-13	-12	-6
A	-8	-4	5	1	-3	-7
T	-12	-8	1	0	11	7
A	-16	-12	2	11	7	6
C	-20	-16	-2	7	11	**17**

GA-ATC
CATA-C

One best traceback

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0	-4	-8	-12	-16	-20
C	-4	-5	-9	-13	-12	-6
A	-8	-4	5	1	-3	-7
T	-12	-8	1	0	11	7
A	-16	-12	2	11	7	6
C	-20	-16	-2	7	11	**17**

GAAT-C
-CATAC

Another best traceback

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0	-4	-8	-12	-16	-20
C	-4	-5	-9	-13	-12	-6
A	-8	-4	5	1	-3	-7
T	-12	-8	1	0	11	7
A	-16	-12	2	11	7	6
C	-20	-16	-2	7	11	**17**

GAAT-C
-CATAC

GA-ATC
CATA-C

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		G	A	A	T	C
	0	-4	-8	-12	-16	-20
C	-4	-5	-9	-13	-12	-6
A	-8	-4	5	1	-3	-7
T	-12	-8	1	0	11	7
A	-16	-12	2	11	7	6
C	-20	-16	-2	7	11	**17**

Multiple solutions

GA-ATC
CATA-C

GAAT-C
CA-TAC

GAAT-C
C-ATAC

GAAT-C
-CATAC

- When a program returns a single sequence alignment, it may not be the **only** best alignment but it is guaranteed to be one of them.
- In our example, all of the alignments at the left have equal scores.

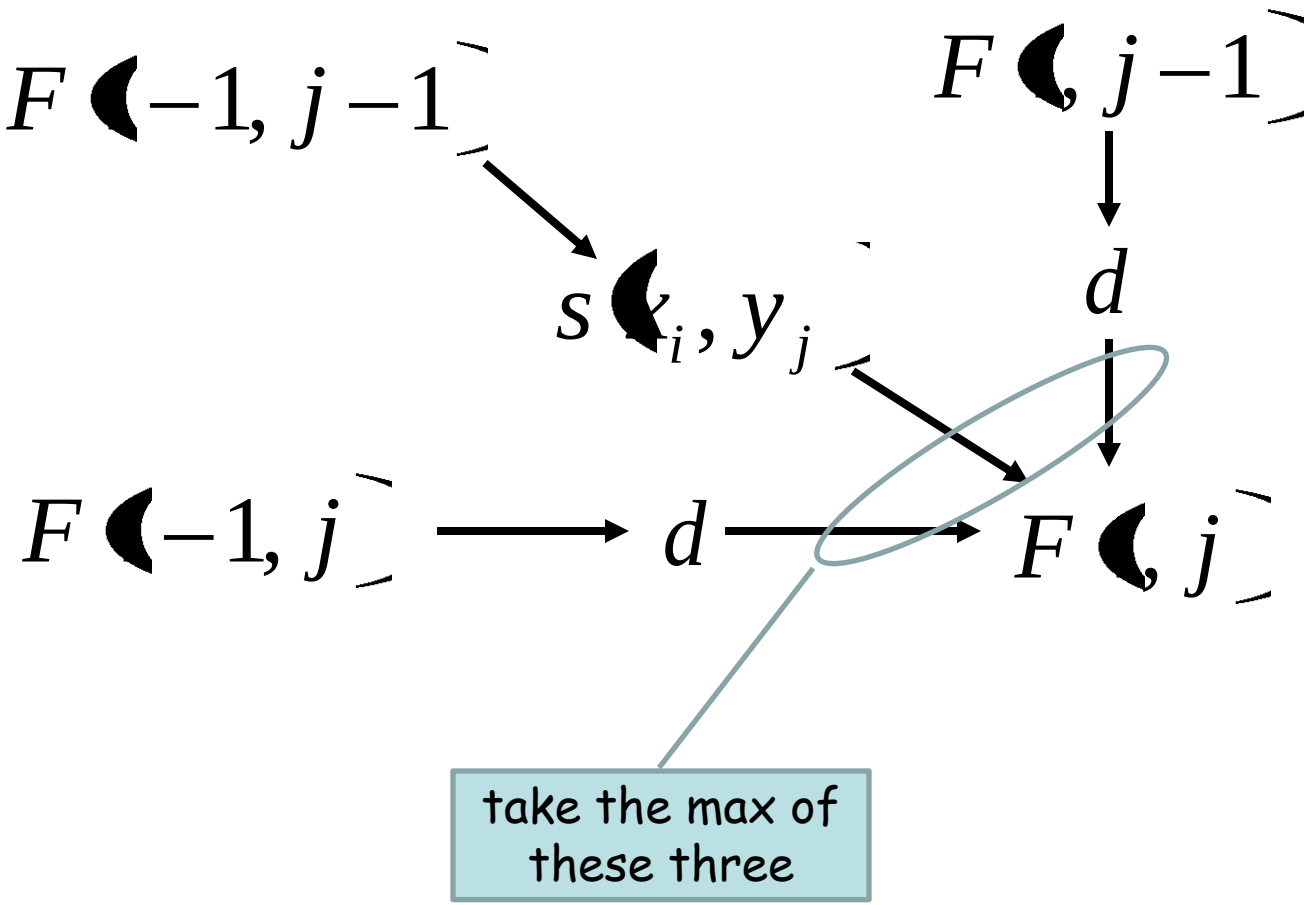
DP in equation form

- Align sequence x and y.
- F is the DP matrix; s is the substitution matrix; d is the linear gap penalty.

$$F(0,0) = 0$$

$$F(i,j) = \max\begin{cases} F(i-1, j-1) + s(x_i, y_j) \\ F(i-1, j) + d \\ F(i, j-1) + d \end{cases}$$

DP equation graphically



Dynamic programming

- Yes, it's a weird name.
- DP is closely related to recursion and to mathematical induction.
- We can prove that the resulting score is optimal.

What you should know

- Scoring a pairwise alignment requires a substitution matrix and gap penalties.
- Dynamic programming (DP) is an efficient algorithm for finding an optimal alignment.
- Entry (`i`,`j`) in the DP matrix stores the score of the best-scoring alignment up to that position.
- DP iteratively fills in the matrix using a simple mathematical rule.
- How to use DP to find an alignment.

Practice problem: find a best pairwise alignment of *GAATC* and *AATTC*

	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

d = -4

		G	A	A	T	C
	0					
A						
A						
T						
T						
C						