Sequence Comparison: Dynamic Programming

Genome 373

Genomic Informatics

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GAATC
CATAC

Mission:

Find the best alignment between two sequences.

A "search" algorithm for finding the alignment with the best score

- Dynamic programming

A method for scoring alignments

- Substitution matrix
- Gap penalties

Scoring Aligned Bases

- **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

Purine	A	G
Pyrimidine	C	T

- **Substitution matrix:**
  - **Linear** gap penalty
  - **Affine** gap penalty

GAAT−C **d=−4**

CA−TAC

-5 + 10 + -4 + 10 + -4 + 10 = 17

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 possible alignments of two sequences of length ***n*** exist?

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

2n choose n
the binomial coefficient

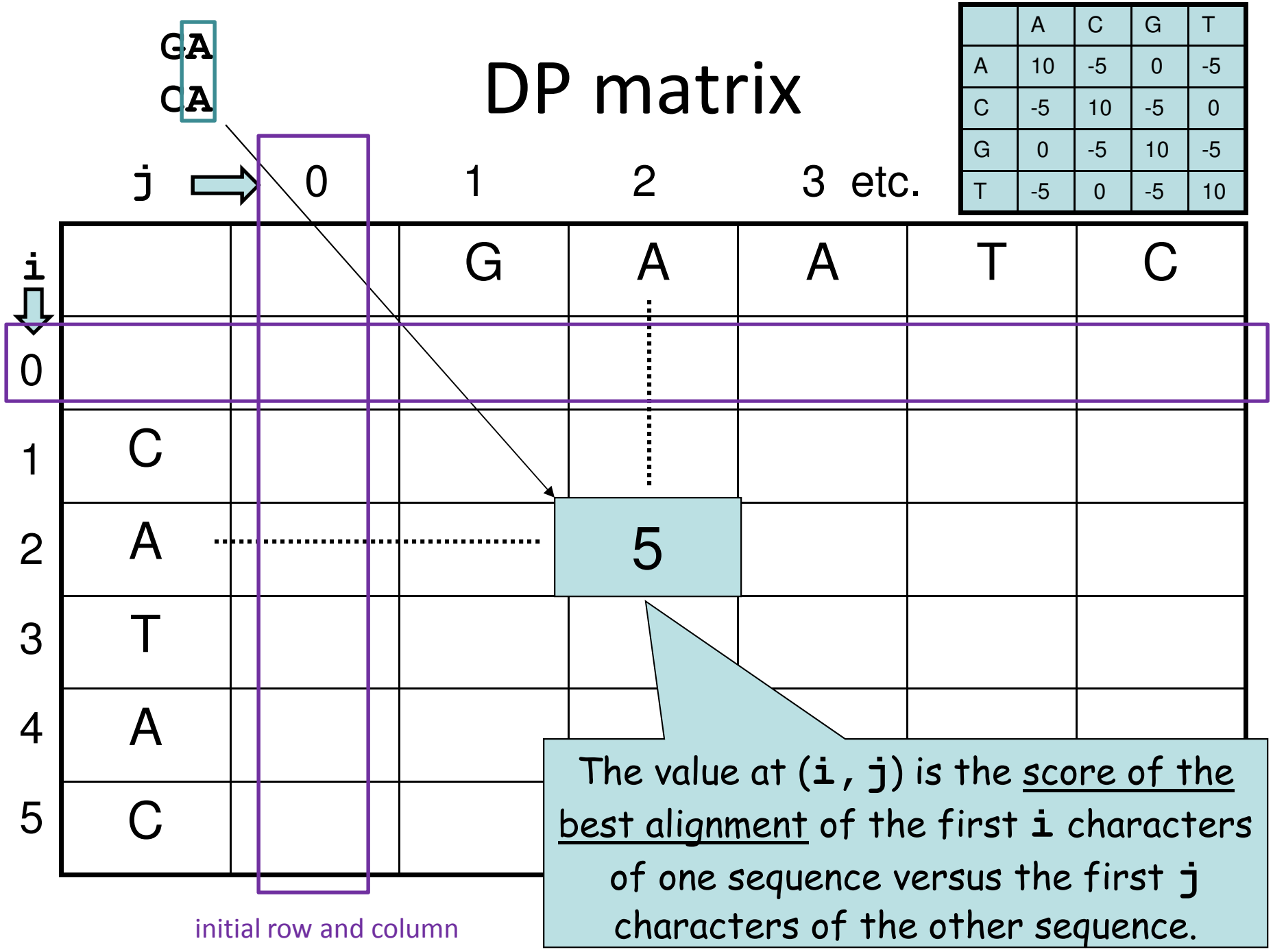
5	2.5×10^2
10	1.8×10^5
20	1.4×10^{11}
30	1.2×10^{17}
40	1.1×10^{23}

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

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

The Needleman–Wunsch Algorithm

- An algorithm for **global alignment** on two sequences
- A **Dynamic Programming (DP)** approach
  - 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.



	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						

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

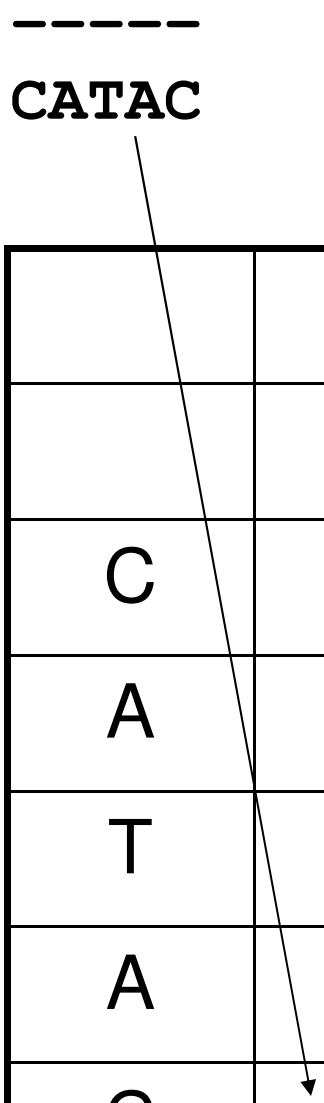
	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

		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					



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 →	-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**

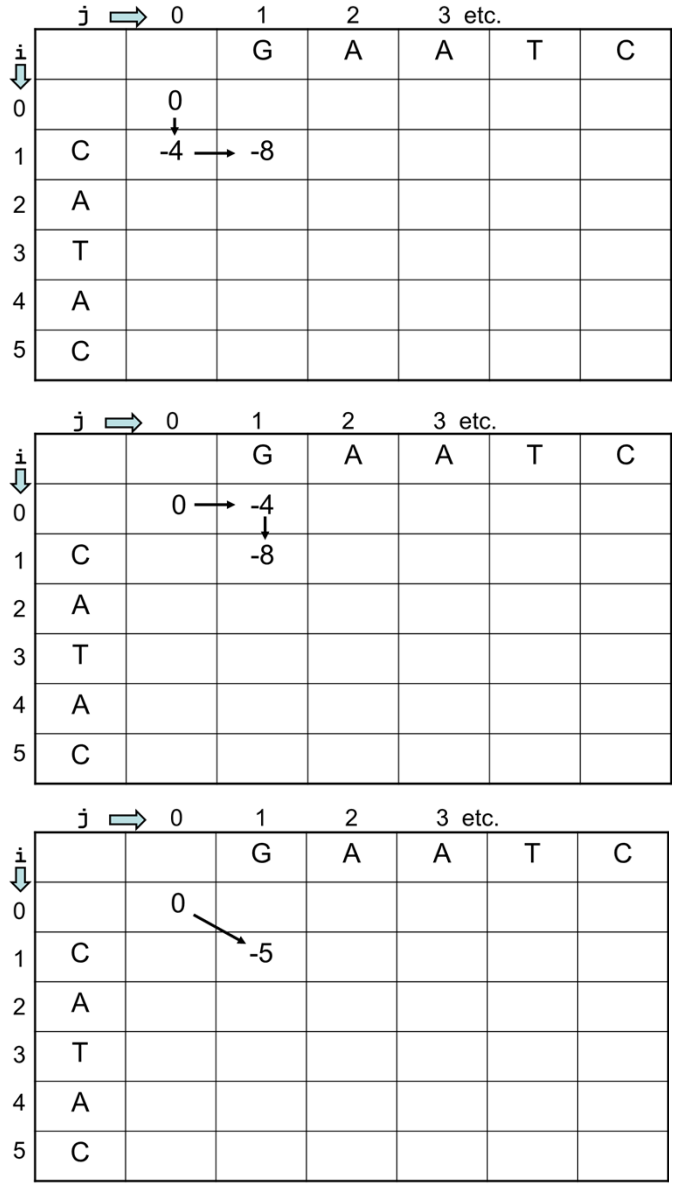
	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

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						

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



Which of these three ways should we use?

Accept the highest scoring of the three

Accept the highest scoring of the three

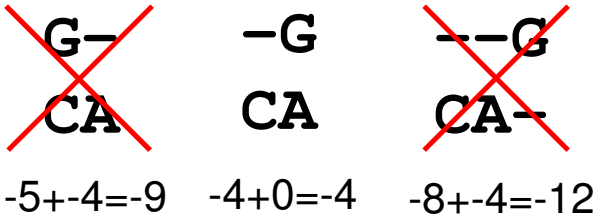
	A	C	G	T
A	10	-5	0	-5
C	-5	10	-5	0
G	0	-5	10	-5
T	-5	0	-5	10

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

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					

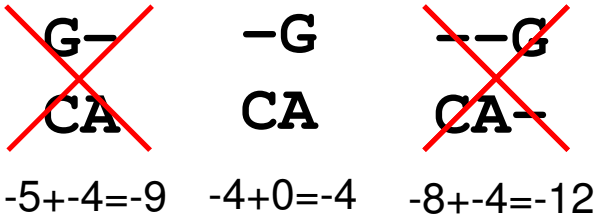


DP matrix

	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



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**

–G–A

CATA

Full Alignment

	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.

Full Alignment

	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**

Full Alignment

	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					-6
A	-8					-7
T	-12	-8	1	0	11	7
A	-16	-12	2	11	7	6
C	-20	-16	-2	7	11	**17**

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

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.

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						