Sequence Analysis (part II)

BBSI 2006: Lecture #(χ+2)

Takis Benos (2006)

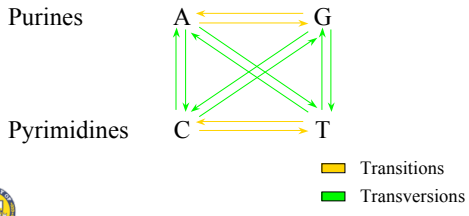
Outline

- Sequence variation
- Distance measures
- Scoring matrices
- Pairwise alignments (global, local)
- Database searches (BLAST, FastA)
- Multiple sequence alignments

Sequence Variations

Sequence variation

- Base mutations: the source of sequence variation



Sequence variation (cntd)

```
tggagctAtt attgctaagt Aacatttacc ccctgaagtt aatgGatcaa tcaagagaga 120
tgtgggctgt aatgaaTcgt Cttattgaat Taacaggttg gatcgttctt gtcgtttcag 180
          M   N   R   L   I   E   L
tcattcttct tggcgtggcg agtcacattg acaactatca gccacctgaa cagagtgctt 240
cggtacaaca caagtaagct ctgcacttgt ggagcgacat gctgcccgtc cgggtgcatg 300
```

silent missense nonsense

```
tggagctGtt attgctaagt Tacatttacc ccctgaagtt aatgAatcaa tcaagagaga 120
tgtgggctgt aatgaaCcgt Gttattgaat Aaacaggttg gatcgttctt gtcgtttcag 180
          M   N   R   V   I   E
tcattcttct tggcgtggcg agtcacattg acaactatca gccacctgaa cagagtgctt 240
cggtacaaca caagtaagct ctgcacttgt ggagcgacat gctgcccgtc cgggtgcatg 300
```


Sequence variation (cntd)

```
tggagctAtt attgctaagt Aacatttacc ccctgaagtt aatgGatcaa tcaagagaga 120
tgtgggctgt aatgaaTcgt Cttattgaat taacaggttg gatcgttctt gtcgtttcag 180
          M   N   R   L   I   E   L
tcattcttct tggcgtggcg agtcacattg acaactatca gccacctgaa cagagtgctt 240
cggtacaaca caagtaagct ctgcacttgt ggagcgacat gctgcccgtc cgggtgcatg 300
```

deletion

```
tggagctGtt attgctaagt Tacatttacc ccctgaagtt aatgAatcaa tcaagagaga 120
tgtgggctgt aatgaaCcgt Gttattgaa- taacaggttg gatcgttctt gtcgtttcag 180
          M   N   R   V   I   E
tcattcttct tggcgtggcg agtcacattg acaactatca gccacctgaa cagagtgctt 240
cggtacaaca caagtaagct ctgcacttgt ggagcgacat gctgcccgtc cgggtgcatg 300
```

Sequence variation (cntd)

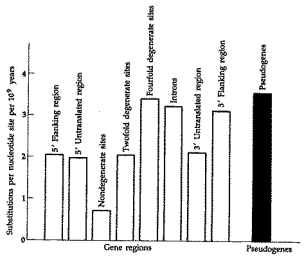


Figure 2. Average rates of substitution in different parts of genes and in pseudogenes.

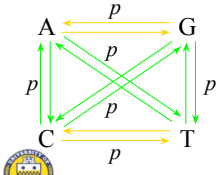
Source: Li & Graur "Fundamentals of Molecular Evolution", 1991, Sinauer Assoc.

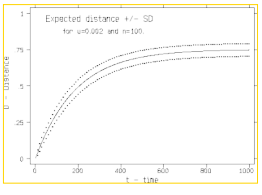
Distance measures

Nucleic acid distances

- No selection - no correction:

$$D = k / N$$



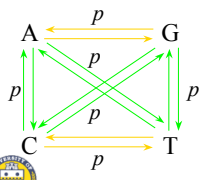


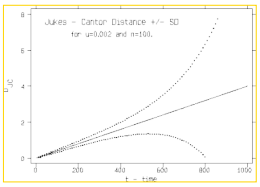
Source: http://helix.biology.mcmaster.ca/721/distance/distance.html.

Nucleic acid distances (cntd)

- Jukes-Cantor correction:

$$D_{JC} = -0.75 \ln (1 - D/0.75)$$



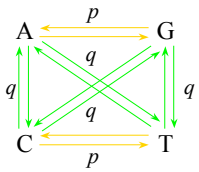


Source: http://helix.biology.mcmaster.ca/721/distance/distance.html.

Nucleic acid distances (cntd)

- Kimura's 2-parameter model:

$$D_{K2P} = -0.5 \ln (1 - 2P - 2Q) - 0.25 \ln(1 - 2Q)$$



Source: http://helix.biology.mcmaster.ca/721/distance/distance.html.

Scoring matrices

Nucleic acid distances (cntd)

- Nucleotide substitution matrices.

	A	T	C	G
A	1	0	0	0
T	0	1	0	0
C	0	0	1	0
G	0	0	0	1

Identity

	A	T	C	G
A	5	-4	-4	-4
T	-4	5	-4	-4
C	-4	-4	5	-4
G	-4	-4	-4	5

BLAST

	A	T	C	G
A	0	5	5	1
T	5	0	1	5
C	5	1	0	5
G	1	5	5	0

Transition/ Transversion

Amino acid distances: PAM

- **P**ercent **A**ccepted **M**utations (PAM) matrices:
  - Frequency substitution matrix from aligned sequences (Dayhoff, 1978).
  - M(*i*,*j*): no. of a.a. *i* to *j* mutations
  - 71 groups of closely related proteins *(why?)*; 1,572 changes.
  - PAM*n*: the aligned sequences have *n* a.a. substitutions per 100 residues.

Amino acid distances: PAM (cntd)

- Assumptions of the PAM model:
  - Replacement at any site depends only on the a.a. on that site, given the mutability table.
  - Sequences in the training set (and those compared) have average a.a. composition.

Amino acid distances: PAM (cntd)

Table 1 - The log odds matrix for 250 PAMs (multiplied by 10)

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
A	2	-2	0	0	-4	1	-1	-1	-1	-2	-1	0	1	0	-2	1	1	0	-6	-3
C		12	-5	-5	-4	-3	-3	-2	-5	-6	-5	-4	-3	-5	-4	0	-2	-2	-8	0
D			4	3	-6	1	1	-2	0	-4	-3	2	-1	2	-1	0	0	-2	-7	-4
E				4	-5	0	1	-2	0	-3	-2	1	-1	2	-1	0	0	-2	-7	-4
F					9	-5	-2	1	-5	2	0	-4	-5	-5	-4	-3	-3	-1	0	7
G						5	-2	-3	-2	-4	-3	0	-1	-1	-3	1	0	-1	-7	-5
H							6	-2	0	-2	-2	2	0	3	2	-1	-1	-2	-3	0
I								5	-2	2	2	-2	-2	-2	-2	-1	0	4	-5	-1
K									5	-3	0	1	-1	1	3	0	0	-2	-3	-4
L										6	4	-3	-3	-2	-3	-3	-2	2	-2	-1
M											6	-2	-2	-1	0	-2	-1	2	-4	-2
N												2	-1	1	0	1	0	-2	-4	-2
P													6	0	0	1	0	-1	-6	-5
Q														4	1	-1	-1	-2	-5	-4
R															6	0	-1	-2	2	-4
S																2	1	-1	-2	-3
T																	3	0	-5	-3
V																		4	-6	-2
W																			17	0
Y																				10

Source: http://helix.biology.mcmaster.ca/721/distance/node9.html

$$Score(i,j) = \log_{10} M(i,j)/f(i)$$

Amino acid distances: PAM (cntd)

- Sources of error in the PAM model:
  - Many proteins depart from the average a.a. composition.
  - The a.a. composition can vary even within a protein (e.g., transmembrane proteins).
  - A.a. positions are not "mutated" equally probably; especially in long evolutionary distances.

Amino acid distances: PAM (cntd)

- Sources of error in the PAM model *(cntd)*:
  - Rare replacements are observed too infrequently and…
  - …errors in PAM1 are magnified in PAM250.

A.a. distances: BLOSUM

- **Blo**cks **Su**bstitution **M**atrices (BLOSUM):
  - Log-likelihood matrix (Henikoff & Henikoff, 1992)
  - BLOCKS database of aligned sequences used as primary source set.

A.a. distances: BLOSUM (cntd)

```
AKAGDA---GGCDA
DRALDAFG-GSSDA
GKLGDAI--GSSAF
AKAGGA---GGTAG
CRIGFRC-DGTTDH
AKAKDA--DHSSCI
```

$Score(i,j) = 2 \log_2 q_{i,j} / e_{i,j}$

$e_{i,j} = p_i^2$ *for* $i=j$

$e_{i,j} = 2\, p_i\, p_j$ *for* $i \neq j$

$p_i = 0.5\, (q_{ii} + \sum q_{ij})$

A.a. distances: BLOSUM (cntd)

- Weighted contribution of similar(*) sequences in order to reduce redundancy.
- BLOSUM62 is more closely related to PAM120.

(*) *n*% similar; the *n* in BLOSUM*n*

A.a. distances: BLOSUM (cntd)

Table 2 - The log odds matrix for BLOSUM 62

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
A	4	0	-2	-1	-2	0	-2	-1	-1	-1	-1	-2	-1	-1	-1	1	0	0	-3	-2
C		9	-3	-4	-2	-3	-3	-1	-3	-1	-1	-3	-3	-3	-3	-1	-1	-1	-2	-2
D			6	2	-3	-1	-1	-3	-1	-4	-3	1	-1	0	-2	0	-1	-3	-4	-3
E				5	-3	-2	0	-3	1	-3	-2	0	-1	2	0	0	-1	-2	-3	-2
F					6	-3	-1	0	-3	0	0	-3	-4	-3	-3	-2	-2	-1	1	3
G						6	-2	-4	-2	-4	-3	0	-2	-2	-2	0	-2	-3	-2	-3
H							8	-3	-1	-3	-2	1	-2	0	0	-1	-2	-3	-2	2
I								4	-3	2	1	-3	-3	-3	-3	-2	-1	3	-3	-1
K									5	-2	-1	0	-1	1	2	0	-1	-2	-3	-2
L										4	2	-3	-3	-2	-2	-2	-1	1	-2	-1
M											5	-2	-2	0	-1	-1	-1	1	-1	-1
N												6	-2	0	0	1	0	-3	-4	-2
P													7	-1	-2	-1	-1	-2	-4	-3
Q														5	1	0	-1	-2	-2	-1
R															5	-1	-1	-3	-3	-2
S																4	1	-2	-3	-2
T																	5	0	-2	-2
V																		4	-3	-1
W																			11	2
Y																				7

Source: http://helix.biology.mcmaster.ca/721/distance/node10.html

Substitution matrices: comparison

- PAM *vs* BLOSUM

BLOSUM 80	BLOSUM 62	BLOSUM 45
PAM 1	PAM 120	PAM 250
Less divergent	← →	*More divergent*

Source: http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/Scoring2.html

- Matrices of choice:
  - BLOSUM62: the all-weather matrix
  - PAM250: for distant relatives

Substit. matrices: comparison (cntd)

- PAM *vs* BLOSUM *(cntd)*
  - Lower PAM/higher BLOSUM matrices identify shorter local alignments of highly similar sequences
  - Higher PAM/lower BLOSUM matrices identify longer local alignments of more distant sequences

Substit. matrices: comparison (cntd)

PAM10

```
A  7
R -10   9
N  -7  -9   9
D  -6 -17  -1   8
C -10 -11 -17 -21  10
Q  -7  -4  -7  -6 -20   9
E  -5 -15  -5   0 -20  -1   8
G  -4 -13  -6  -6 -13 -10  -7   7
H -11  -4  -2  -7 -10  -2  -9 -13  10
I  -8  -8  -8 -11  -9 -11  -8 -17 -13   9
L  -9 -12 -10 -19 -21  -8 -13 -14  -9  -4   7
K -10  -2  -4  -8 -20  -6  -7 -10 -10  -9 -11   7
M  -8  -7 -15 -17 -20  -7 -10 -12 -17  -3  -2  -4  12
F -12 -12 -12 -21 -19 -19 -20 -12  -9  -5  -5 -20  -7   9
P  -4  -7  -9 -12 -11  -6  -9 -10  -7 -12 -10 -10 -11 -13   8
S  -3  -6  -2  -7  -6  -8  -7  -4  -9 -10 -12  -7  -8  -9  -4   7
T  -3 -10  -5  -8 -11  -9  -9 -10 -11  -5 -10  -6  -7 -12  -7  -2   8
W -20  -5 -11 -21 -22 -19 -23 -21 -10 -20  -9 -18 -19  -7 -20  -8 -19  13
Y -11 -14  -7 -17  -7 -18 -11 -20  -6  -9 -10 -12 -17  -1 -20 -10  -9  -8  10
V  -5 -11 -12 -11  -9 -10 -10  -9  -9  -1  -5 -13  -4 -12  -9 -10  -6 -22 -10   8
   A   R   N   D   C   Q   E   G   H   I   L   K   M   F   P   S   T   W   Y   V
```

Substit. matrices: comparison (cntd)

PAM250

```
A  2
R -2   6
N  0   0   2
D  0  -1   2   4
C -2  -4  -4  -5  12
Q  0   1   1   2  -5   4
E  0  -1   1   3  -5   2   4
G  1  -3   0   1  -3  -1   0   5
H -1   2   2   1  -3   3   1  -2   6
I -1  -2  -2  -2  -2  -2  -2  -3  -2   5
L -2  -3  -4  -6  -2  -3  -4  -2   2   6
K -1   3   1   0  -5   1   0  -2   0  -2  -3   5
M -1   0  -2  -3  -5  -1  -2  -3  -2   2   4   0   6
F -3  -4  -3  -6  -4  -5  -5  -5  -2   1   2  -5   0   9
P  1   0   0  -1  -3   0  -1   0   0  -2  -3  -1  -2  -5   6
S  1   0   1   0   0  -1   0   1  -1  -1  -3   0  -2  -3   1   2
T  1  -1   0   0  -2  -1   0   0  -1   0  -2   0  -1  -3   0   1   3
W -6   2  -4  -7  -8  -5  -7  -7  -3  -5  -2  -3  -4   0  -6  -2  -5  17
Y -3  -4  -2  -4   0  -4  -4  -5   0  -1  -1  -4  -2   7  -5  -3  -3   0  10
V  0  -2  -2  -2  -2  -2  -2  -1  -2   4   2  -2   2  -1  -1  -1   0  -6  -2   4
   A   R   N   D   C   Q   E   G   H   I   L   K   M   F   P   S   T   W   Y   V
```

Substit. matrices: comparison (cntd)

BLOSUM62

```
A  4
R -1   5
N -2   0   6
D -2  -2   1   6
C  0  -3  -3  -3   9
Q -1   1   0   0  -3   5
E -1   0   0   2  -4   2   5
G  0  -2   0  -1  -3  -2  -2   6
H -2   0   1  -1  -3   0   0  -2   8
I -1  -3  -3  -3  -1  -3  -3  -4  -3   4
L -1  -2  -3  -4  -1  -2  -3  -4  -3   2   4
K -1   2   0  -1  -3   1   1  -2  -1  -3  -2   5
M -1  -1  -2  -3  -1   0  -2  -3  -2   1   2  -1   5
F -2  -3  -3  -3  -2  -3  -3  -3  -1   0   0  -3   0   6
P -1  -2  -2  -1  -3  -1  -1  -2  -2  -3  -3  -1  -2  -4   7
S  1  -1   1   0  -1   0   0   0  -1  -2  -2   0  -1  -2  -1   4
T  0  -1   0  -1  -1  -1  -1  -2  -2  -1  -1  -1  -1  -2  -1   1   5
W -3  -3  -4  -4  -2  -2  -3  -2  -2  -3  -2  -3  -1   1  -4  -3  -2  11
Y -2  -2  -2  -3  -2  -1  -2  -3   2  -1  -1  -2  -1   3  -3  -2  -2   2   7
V  0  -3  -3  -3  -1  -2  -2  -3  -3   3   1  -2   1  -1  -2  -2   0  -3  -1   4
   A   R   N   D   C   Q   E   G   H   I   L   K   M   F   P   S   T   W   Y   V
```

Pairwise alignments

Alignment: the problem

Given two sequences, *S* and *T*, and a *scoring matrix* find their relative arrangement with the highest "score".

```
Seq. #1: G A A T T C A G T T A
Seq. #2: G G A T C G A
```

Alignment: the problem (cntd)

```
  G A A T T C A G T T A
  | |
G G A T C G A
```

```
G A A T T C A G T T A
|   | |     |
G G A T C G A
```

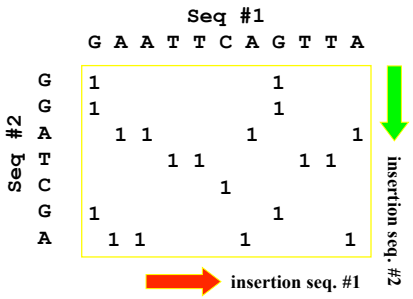
```
G A A T T C - A G T T A
|   |   | |   |
G G A - T C G A
```

Alignment: the problem (cntd)

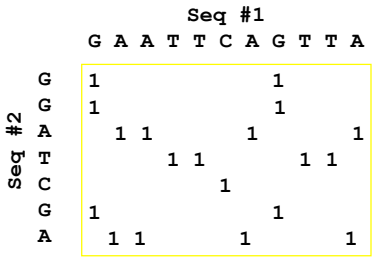
- Scoring schemes: three possible situations…
  - Match REWARD!!
  - Mismatch Penalise???
  - Gap Penalise
    - Gap initiation
    - Gap extension

How much??

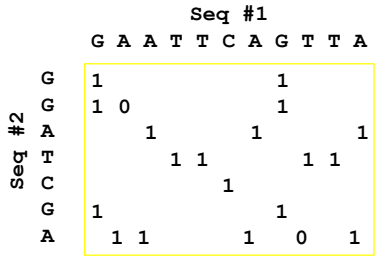
Alignment: a naïve approach



Alignment: a naïve approach



Alignment: a naïve approach (cntd)



Alignment: adding scores

The formula:

$\mathbf{M}_{i,j}$ = **MAXIMUM**{

$\mathbf{M}_{i-1,\,j-1} + \mathbf{S}_{i,j}$ (match/mismatch in the diagonal),

$\mathbf{M}_{i,j-1} + \mathbf{w}$ (gap in sequence #1),

$\mathbf{M}_{i-1,j} + \mathbf{w}$ (gap in sequence #2)

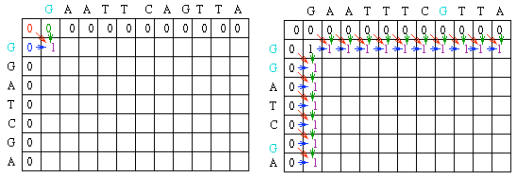
}

- In the following example, the score for match is 1 and for mismatch and gap is 0.

Alignment: adding scores (cntd)

- In each step we need to keep track only the scores of the (*i*,*j*) position and its immediate neighbours: (*i-1*,*j-1*), (*i-1*,*j*) and (*i*,*j-1*).
- We backtrack from the right-down corner to find the actual alignment.

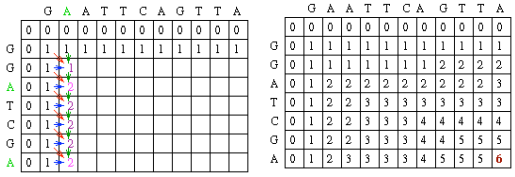
Alignment: adding scores (cntd)



S(1,1) = MAX{
S(0,0)+1=1,
S(0,1)+w=0,
S(1,0)+w=0}=1

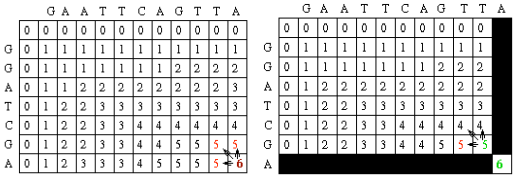
Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/dynamic.html

Alignment: adding scores (cntd)



Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/dynamic.html

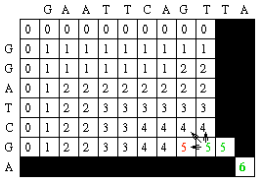
Alignment: adding scores (cntd)




```
Alignment:   (Seq #1)   A
                        |
             (Seq #2)   A
```

Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/dynamic.html

Alignment: adding scores (cntd)

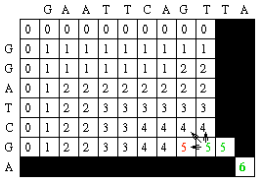


		G	A	A	T	T	C	A	G	T	T	A
	0	0	0	0	0	0	0	0	0	0	0
G	0	1	1	1	1	1	1	1	1	1	1
G	0	1	1	1	1	1	1	1	2	2	2
A	0	1	2	2	2	2	2	2	2	2	2
T	0	1	2	2	3	3	3	3	3	3	3
C	0	1	2	2	3	3	4	4	4	4	4
G	0	1	2	2	3	3	4	4	5	5	5
A											6

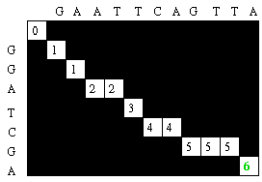
```
                (Seq #1)                T A
Alignment:                              |
                (Seq #2)                - A
```

Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/dynamic.html

Alignment: adding scores (cntd)



		G	A	A	T	T	C	A	G	T	T	A
	0	0	0	0	0	0	0	0	0	0	0
G	0	1	1	1	1	1	1	1	1	1	1
G	0	1	1	1	1	1	1	1	2	2	2
A	0	1	2	2	2	2	2	2	2	2	2
T	0	1	2	2	3	3	3	3	3	3	3
C	0	1	2	2	3	3	4	4	4	4	4
G	0	1	2	2	3	3	4	4	5	5	5
A											6



		G	A	A	T	T	C	A	G	T	T	A
	0										
G		1									
G			1								
A				2	2						
T						3					
C							4	4			
G									5	5	5
A											6

```
                (Seq #1) G A A T T C A G T T A
Alignment:               |   |   | |   |     |
                (Seq #2) G G A - T C - G - - A
```

Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/dynamic.html

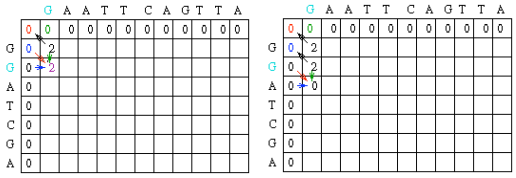
Alignment: another example

The formula:

$M_{i,j}$ = MAXIMUM{
$M_{i-1,j-1}$ + $S_{i,j}$ (match/mismatch in the diagonal),
$M_{i,j-1}$ + w (gap in sequence #1),
$M_{i-1,j}$ + w (gap in sequence #2)
}

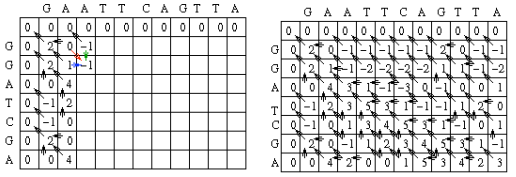
- New scores: 2 for match, -1 for mismatch and -2 for gap.

Alignment: another example (cntd)



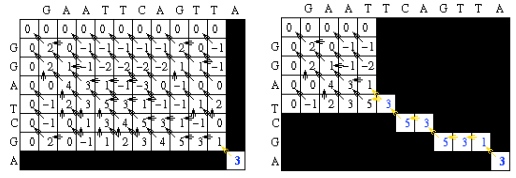
Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/adv_dynamic.html

Alignment: another example (cntd)



Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/adv_dynamic.html

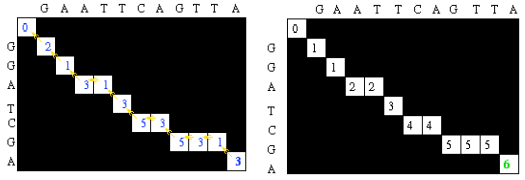
Alignment: another example (cntd)



```
Alignment:   (Seq #1)   T C A G T T A
                        | |   |     |
             (Seq #2)   T C - G - - A
```

Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/adv_dynamic.html

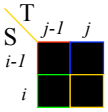
Alignment: another example (cntd)




```
Alignment:  (Seq #1) G A A T T C A G T T A
                     |   |   | |   |     |
            (Seq #2) G G A - T C - G - - A
```

Source: http://www.sbc.su.se/~per/molbioinfo2001/dynprog/adv_dynamic.html

Global alignment



PAM

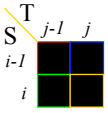
DNA matrix BLOSUM

$$\mathbf{M}_{i,j} = \text{MAX} \begin{cases} \mathbf{M}_{i-1,j-1} + \mathbf{Score}(S_i, T_j) \\ \mathbf{M}_{i,j-1} + \mathbf{w} \\ \mathbf{M}_{i-1,j} + \mathbf{w} \end{cases}$$

Gap penalty

Needleman & Wunsch, 1970

Local alignment



PAM

DNA matrix BLOSUM

$$\mathbf{M}_{i,j} = \text{MAX} \begin{cases} \mathbf{0} \\ \mathbf{M}_{i-1,j-1} + \mathbf{Score}(S_i, T_j) \\ \mathbf{M}_{i,j-1} + \mathbf{w} \\ \mathbf{M}_{i-1,j} + \mathbf{w} \end{cases}$$

Gap penalty

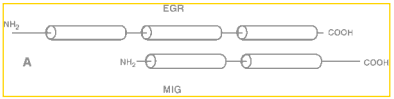
Smith & Waterman, 1981

Local alignment

Given two sequences, *S* and *T*, find two subsequences, *s* and *t*, whose alignment has the highest "score" amongst all subsequence pairs.

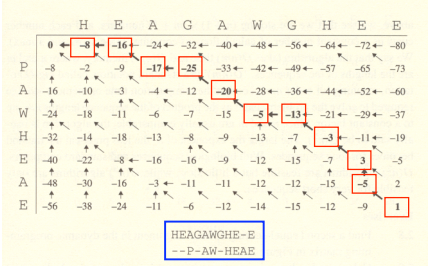
Why do we need local alignment, if we have the global one?

Local alignment: an example



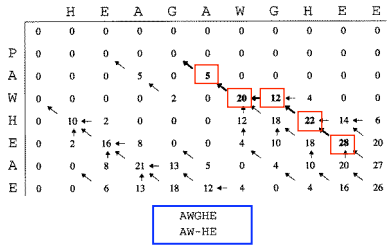

```
EGR4_HUMAN    KA [FACPVESCVRSFARSDELNRHLRIH] TGHKP [FQCRICLRNFSRSDHLTSHVRTH] TGEKP [FACDV--CGRRFARSDERKRHSKVH]
EGR4_RAT      KA [FACPVESCVRTFARSDELNRHLRIH] TGHKP [FQCRICLRNFSRSDHLTTHVRTH] TGEKP [FACDV--CGRRFARSDERKRHSKVH]
EGR3_HUMAN    RP [HACPAEGCDRRFSRSDELTRHLRIH] TGHKP [FQCRICMRSFSRSDHLTTHIRTH] TGEKP [FACEP--CGRKFARSDERKRHAKIH]
EGR3_RAT      RP [HACPAEGCDRRFSRSDELTRHLRIH] TGHKP [FQCRICMRSFSRSDHLTTHIRTH] TGEKP [FACEP--CGRKFARSDERKRHAKIH]
EGR1_HUMAN    RP [VACPVESCDRRFSRSDELTRHIRIH] TGQKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDI--CGRKFARSDERKRHTKIH]
EGR1_MOUSE    RP [VACPVESCDRRFSRSDELTRHIRIH] TGQKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDI--CGRKFARSDERKRHTKIH]
EGR1_RAT      RP [VACPVESCDRRFSRSDELTRHIRIH] TGQKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDI--CGRKFARSDERKRHTKIH]
EGR1_BRARE    RP [VACPVETCDRRFSRSDELTRHIRIH] TGQKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACEI--CGRKFARSDERKRHTKIH]
EGR2_RAT      RP [VPCPAEGCDRRFSRSDELTRHIRIH] TGHKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDV--CGRKFARSDERKRHTKIH]
EGR2_XENLA    RP [VPCPAEGCDRRFSRSDELTRHIRIH] TGHKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDV--CGRKFARSDERKRHTKIH]
EGR2_MOUSE    RP [VPCPAEGCDRRFSRSDELTRHIRIH] TGHKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDV--CGRKFARSDERKRHTKIH]
EGR2_HUMAN    RP [VPCPAEGCDRRFSRSDELTRHIRIH] TGHKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDV--CGRKFARSDERKRHTKIH]
EGR2_BRARE    RP [VPCPAEGCDRRFSRSDELTRHIRIH] TGHKP [FQCRICMRNFSRSDHLTTHIRTH] TGEKP [FACDP--CGRKFARSDERKRHTKIH]
MIG1_KLULA    -- [----------------------] ----RP [YVCPICQRGFHRLEHQTRHIRTH] TGERP [HACDFPGCSKRFSRSDELTRHRRIH]
MIG1_KLUMA    -- [----------------------] ----RP [YNCPICHRGFHRLEHQTRHIRTH] TGERP [HACDFPGCARKFSRSDELTRHRRIH]
MIG1_YEAST    -- [----------------------] ----RP [HACPICHRAFHRLEHQTRHMRIH] TGEKP [HACDFPGCVKRFSRSDELTRHRRIH]
MIG2_YEAST    -- [----------------------] ----RP [FRCDTCHRGFHRLEHKKRHLRTH] TGEKP [HRCAFPGCGKSFSRSDELKRHRTH]
                 [                      ]    :P [.*  * * * * *.* . *:* *] ***:* [.*    * : *:*** .** : *]
```


Local vs. global alignment



Source: Durbin et al "Biological Sequence Analysis", 1998, Cambridge University Press

Local vs. global alignment (cntd)



Source: Durbin et al "Biological Sequence Analysis", 1998, Cambridge University Press

Local alignment (cntd)

- Characteristics of local alignments:
  - The alignment can start/end at any point in the matrix.
  - No negative scores.
  - The mean value of the scoring matrix (e.g. PAM, BLOSUM) should be negative.
  - There should be positive scores in the scoring matrix.