Dynamic Programming Method for Analyzing Biomolecular Sequences

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Outline

- The paradigm of dynamic programming
- Sequence alignment – a general framework for comparing sequences in bioinformatics
- Dynamic programming algorithms for sequence alignment
- Techniques for improving the efficiency of the algorithms
- Multiple sequence alignment

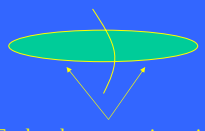
Dynamic Programming

- Dynamic programming is an algorithmic method for solving optimization problems with a compositional/recursive cost structure.
- Richard Bellman was one of the principal founders of this approach.

Two key ingredients

- Two key ingredients for an optimization problem to be suitable for a dynamic programming solution:

1. optimal substructures



Each substructure is optimal.

(principle of optimality)

2. overlapping subinstances

Subinstances are dependent.

(Otherwise, a divide-and-conquer approach is the choice.)

Three basic components

- The development of a dynamic programming algorithm has three basic components:
  - A recurrence relation (for defining the value/cost of an optimal solution);
  - A tabular computation (for computing the value of an optimal solution);
  - A backtracing procedure (for delivering an optimal solution).

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Fibonacci numbers

The *Fibonacci numbers* are defined by the following recurrence:

$$F_0 = 0$$
$$F_1 = 1$$
$$F_i = F_{i-1} + F_{i-2} \quad \text{for } i > 1.$$

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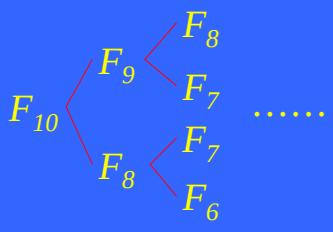
How to compute F_{10} ?



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Tabular computation

- Tabular computation can avoid redundant computation steps.

F_0	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
0	1	1	2	3	5	8	13	21	34	55

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Maximum sum interval

- Given a sequence of real numbers $a_1 a_2 \ldots a_n$, find a consecutive subsequence with the maximum sum.

```
9 -3 1 7 -15 2 3 -4 2 -7 6 -2 8 4 -9
```

For each position, we can compute the maximum-sum interval starting at that position in $O(n)$ time. Therefore, a naive algorithm runs in $O(n^2)$ time.

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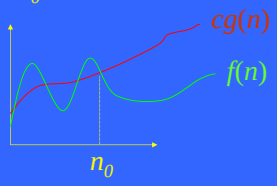
O-notation: an asymptotic upper bound

- $f(n) = O(g(n))$ iff there exist two positive constant c and n_0 such that $0 \le f(n) \le cg(n)$ for all $n \ge n_0$



For example, $5n + 108 = O(n)$ and $2n = O(n \log n)$.

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How functions grow?

function / n	$30n$	$92n \log n$	$26n^2$	$0.68n^3$	2^n
100	0.003 sec.	0.003 sec.	0.26 sec.	0.68 sec.	4×10^{16} yr.
100,000	3.0 sec.	2.6 min.	3.0 days	22 yr.	

(Assume one million operations per second.)

For large data sets, algorithms with a complexity greater than $O(n \log n)$ are often impractical!

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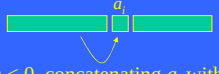
Maximum sum interval (the recurrence relation)

- Define $S(i)$ to be the maximum sum of the intervals ending at position i.

$$S(i) \leftarrow a_i + \max \begin{cases} S(i-1) \\ 0 \end{cases}$$



If $S(i\text{-}1) < 0$, concatenating a_i with its previous interval gives less sum than a_i itself.

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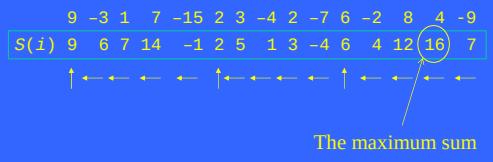
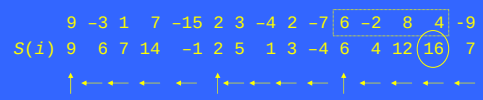
Maximum sum interval (tabular computation)



Maximum sum interval (backtracing)



The maximum-sum interval: 6 -2 8 4

Running time: O(n).

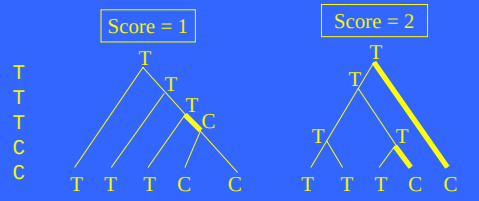
Defining scores for alignment columns

- *infocon* [Stojanovic *et al.*, 1999]
  - Each column is assigned a score that measures its information content, based on the frequencies of the letters both within the column and within the alignment.

```
CGGATCAT–GGA
CTTAACATTGAA
GAGAACATAGTA
```


Defining scores (cont'd)

- *phylogen* [Stojanovic *et al.*, 1999]
  - columns are scored based on the evolutionary relationships among the sequences implied by a supplied phylogenetic tree.



Two fundamental problems we solved (joint work with Lin and Chao)

- Given a sequence of real numbers of length n and an upper bound U, find a consecutive subsequence of length at most U with the maximum sum --- an $O(n)$-time algorithm.

$U = 3$

9 –3 1 7 –15 2 3 –4 2 –7 6 –2 8 4 -9

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Two fundamental problems we solved (joint work with Lin and Chao)

- Given a sequence of real numbers of length n and a lower bound L, find a consecutive subsequence of length at least L with the maximum average --- an $O(n \log L)$-time algorithm. This has been improved to $O(n)$ by others later.

$L = 4$

3 2 14 6 6 2 10 2 6 6 14 2 1

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Another example

Given a sequence as follows:

2, 6.6, 6.6, 3, 7, 6, 7, 2

and $L = 2$, the highest-average interval is the squared area, which has the average value 20/3.

2, 6.6, 6.6, 3, 7, 6, 7, 2

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GC-rich regions

- Our method can be used to locate a region of length at least L with the highest C+G ratio in $O(n \log L)$ time.

ATGACTCGAGCTCGTCA

00101011011011010 ← Search for an interval of length at least L with the highest average.

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Length-unconstrained version

- Maximum average interval

3 2 14 6 6 2 10 2 6 6 14 2 1

The maximum element is the answer. It can be done in $O(n)$ time.

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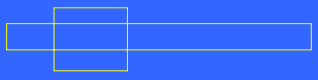
A naive algorithm

- A simple shift algorithm can compute the highest-average interval of a fixed length in $O(n)$ time



- Try L, $L+1$, $L+2$, ..., n. In total, $O(n^2)$.

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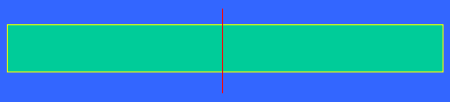
A pigeonhole principle

- Notice that the length of an optimal interval is bounded by $2L$, we immediately have an $O(nL)$-time algorithm.



We can bisect a region of length >= $2L$ into two segments, where each of them is of length >= L.

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Future Development

- Best k (nonintersecting) subsequences?
- Max-average with both upper and lower length bounds
- General (gapped) local alignment with length upper bound.
- Measurement of goodness?

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Longest increasing subsequence (LIS)

- The longest increasing subsequence is to find a longest increasing subsequence of a given sequence of distinct integers $a_1 a_2 \ldots a_n$.

e.g. 9 2 5 3 7 11 8 10 13 6

2 3 7

5 7 10 13 } are increasing subsequences.

We want to find a longest one.

9 7 11

3 5 11 13 } are not increasing subsequences.

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A naive approach for LIS

- Let $L[i]$ be the length of a longest increasing subsequence ending at position i.

$L[i] = 1 + \max_{j = 0..i-1}\{L[j] \mid a_j < a_i\}$
(use a dummy a_0 = minimum, and $L[0]=0$)

9 2 5 3 7 11 8 10 13 6

$L[i]$ 1 1 2 2 3 4 ?

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A naive approach for LIS

$L[i] = 1 + \max_{j = 0..i-1}\{L[j] \mid a_j < a_i\}$

9 2 5 3 7 11 8 10 13 6

$L[i]$ 1 1 2 2 3 4 4 5 6 3

The maximum length

The subsequence 2, 3, 7, 8, 10, 13 is a longest increasing subsequence.

This method runs in $O(n^2)$ time.

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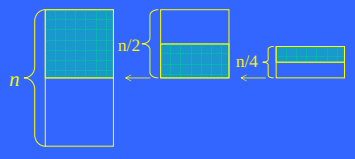
Binary Search

- Given an ordered sequence $x_1 x_2 \ldots x_n$, where $x_1 < x_2 < \ldots < x_n$, and a number y, a binary search finds the largest x_i such that $x_i < y$ in $O(\log n)$ time.



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Binary Search

- How many steps would a binary search reduce the problem size to *1*?

$n \quad n/2 \quad n/4 \quad n/8 \quad n/16 \quad \ldots \quad 1$

How many steps? $O(\log n)$ steps.

$n/2^s = 1$

$\Rightarrow s = \log_2 n$

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An $O(n \log n)$ method for LIS

- Define *BestEnd*[*k*] to be the smallest end number of an increasing subsequence of length *k*.

9 2 5 3 7 11 8 10 13 6

9	2	2	2	2	2	2	2	2	← *BestEnd*[1]
		5	3	3	3	3	3	3	← *BestEnd*[2]
				7	7	7	7	7	← *BestEnd*[3]
					11	8	8	8	← *BestEnd*[4]
							10	10	← *BestEnd*[5]
								13	← *BestEnd*[6]

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An $O(n \log n)$ method for LIS

- Define *BestEnd*[*k*] to be the smallest end number of an increasing subsequence of length *k*.

9 2 5 3 7 11 8 10 13 6

9	2	2	2	2	2	2	2	2	← *BestEnd*[1]
		5	3	3	3	3	3	3	← *BestEnd*[2]
				7	7	7	7	6	← *BestEnd*[3]
					11	8	8	8	← *BestEnd*[4]
							10	10	← *BestEnd*[5]
								13	← *BestEnd*[6]

For each position, we perform a binary search to update *BestEnd*. Therefore, the running time is $O(n \log n)$.

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Longest Common Subsequence (LCS)

- A subsequence of a sequence *S* is obtained by deleting zero or more symbols from *S*. For example, the following are all subsequences of "president": pred, sdn, predent.
- The longest common subsequence problem is to find a maximum length common subsequence between two sequences.

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LCS

For instance,

Sequence 1: president

Sequence 2: providence

Its LCS is priden.

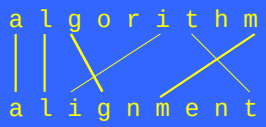
LCS

Another example:

Sequence 1: algorithm

Sequence 2: alignment

One of its LCS is algm.



How to compute LCS?

- Let A=$a_1a_2\ldots a_m$ and $B=b_1b_2\ldots b_n$.
- *len*(*i*, *j*): the length of an LCS between $a_1a_2\ldots a_i$ and $b_1b_2\ldots b_j$
- With proper initializations, *len*(*i*, *j*) can be computed as follows.

$$len(i,j)=\begin{cases}0 & \text{if } i=0 \text{ or } j=0,\\ len(i-1,j-1)+1 & \text{if } i,j>0 \text{ and } a_i=b_j,\\ \max(len(i,j-1),len(i-1,j)) & \text{if } i,j>0 \text{ and } a_i\neq b_j.\end{cases}$$

procedure *LCS-Length(A, B)*

1. **for** $i \leftarrow 0$ **to** m **do** $len(i,0) = 0$
2. **for** $j \leftarrow 1$ **to** n **do** $len(0,j) = 0$
3. **for** $i \leftarrow 1$ **to** m **do**
4. **for** $j \leftarrow 1$ **to** n **do**
5. **if** $a_i = b_j$ **then** $\begin{cases} len(i,j) = len(i-1,j-1)+1 \\ prev(i,j) = \text{"}\nwarrow\text{"} \end{cases}$
6. **else if** $len(i-1,j) \geq len(i,j-1)$
7. **then** $\begin{cases} len(i,j) = len(i-1,j) \\ prev(i,j) = \text{"}\uparrow\text{"} \end{cases}$
8. **else** $\begin{cases} len(i,j) = len(i,j-1) \\ prev(i,j) = \text{"}\leftarrow\text{"} \end{cases}$
9. **return** *len* and *prev*

i	j	0	1 p	2 r	3 o	4 v	5 i	6 d	7 e	8 n	9 c	10 e
0		0	0	0	0	0	0	0	0	0	0	0
1	p	0	↖ 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1
2	r	0	↑ 1	↖ 2	← 2	← 2	← 2	← 2	← 2	← 2	← 2	← 2
3	e	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 2	↑ 2	↖ 3	← 3	← 3	↖ 3
4	s	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 2	↑ 2	↑ 3	↑ 3	↑ 3	↑ 3
5	i	0	↑ 1	↑ 2	↑ 2	↑ 2	↖ 3	← 3	↑ 3	↑ 3	↑ 3	↑ 3
6	d	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↖ 4	← 4	← 4	← 4	← 4
7	e	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↖ 5	← 5	← 5	↖ 5
8	n	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↑ 5	↖ 6	← 6	← 6
9	t	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↑ 5	↑ 6	↑ 6	↑ 6

Running time and memory: O(mn) and O(mn).

The backtracing algorithm

procedure *Output-LCS(A, prev, i, j)*

1 **if** $i = 0$ **or** $j = 0$ **then return**

2 **if** *prev(i, j)=*" ↖ " **then** $\begin{bmatrix} Output - LCS(A, prev, i-1, j-1) \\ \text{print} \quad a_i \end{bmatrix}$

3 **else if** *prev(i, j)=*"↑" **then** *Output-LCS(A, prev, i-1, j)*

4 **else** *Output-LCS(A, prev, i, j-1)*

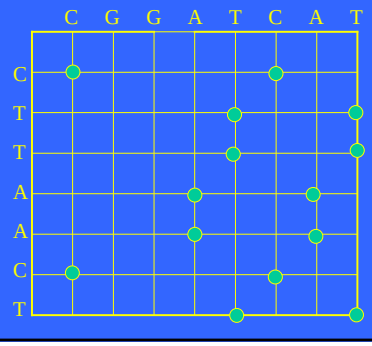
i	j	0	1 p	2 r	3 o	4 v	5 i	6 d	7 e	8 n	9 c	10 e
0		0	0	0	0	0	0	0	0	0	0	0
1	p	0	↖ 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1	← 1
2	r	0	↑ 1	↖ 2	← 2	← 2	← 2	← 2	← 2	← 2	← 2	← 2
3	e	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 2	↑ 2	↖ 3	← 3	← 3	↖ 3
4	s	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 2	↑ 2	↑ 3	↑ 3	↑ 3	↑ 3
5	i	0	↑ 1	↑ 2	↑ 2	↑ 2	↖ 3	← 3	↑ 3	↑ 3	↑ 3	↑ 3
6	d	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↖ 4	← 4	← 4	← 4	← 4
7	e	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↖ 5	← 5	← 5	↖ 5
8	n	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↑ 5	↖ 6	← 6	← 6
9	t	0	↑ 1	↑ 2	↑ 2	↑ 2	↑ 3	↑ 4	↑ 5	↑ 6	↑ 6	↑ 6

Output: *priden*

Dot Matrix

Sequence A：CTTAACT

Sequence B：CGGATCAT



Pairwise Alignment

Sequence A: CTTAACT
Sequence B: CGGATCAT

An alignment of A and B:

```
C---TTAACT  <-- Sequence A
CGGATCA--T  <-- Sequence B
```

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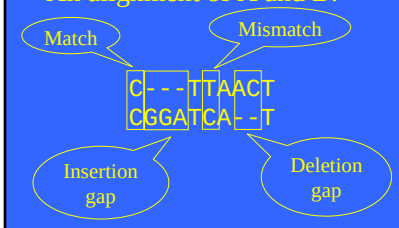
Pairwise Alignment

Sequence A: CTTAACT
Sequence B: CGGATCAT

An alignment of A and B:



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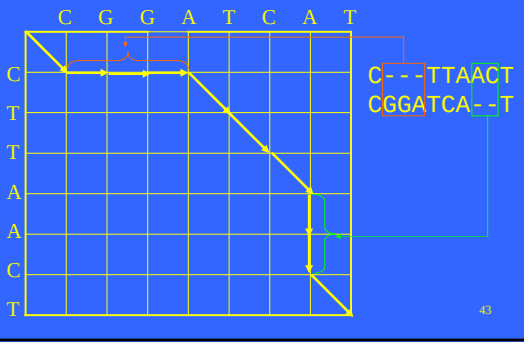
Alignment (or Edit) Graph

Sequence A: CTTAACT

Sequence B: CGGATCAT



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A simple scoring scheme

- Match: +8 ($w(x, y) = 8$, if $x = y$)
- Mismatch: -5 ($w(x, y) = -5$, if $x \neq y$)
- Each gap symbol: -3 ($w(-,x)=w(x,-)=-3$)
  (*i.e.* space)

```
C - - - T T A A C T
C G G A T C A - - T
+8 -3 -3 -3 +8 -5 +8 -3 -3 +8 = +12
```

alignment score

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Scoring Matrices

- Amino acid substitution matrices
  - PAM
  - BLOSUM
- DNA substitution matrices
  - DNA is less conserved than protein sequences
  - Less effective to compare coding regions at nucleotide level

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PAM

- **P**oint **A**ccepted **M**utation (Dayhoff, et al.)
- 1 PAM = PAM_1 = 1% average change of all amino acid positions
  - After 100 PAMs of evolution, not every residue will have changed
    - some residues may have mutated several times
    - some residues may have returned to their original state
    - some residues may not changed at all

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PAM_X

- $PAM_x = PAM_1^x$

  E.g. $PAM_{250} = PAM_1^{250}$
- PAM_{250} is a widely used scoring matrix.

	Ala A	Arg R	Asn N	Asp D	Cys C	Gln Q	Glu E	Gly G	His H	Ile I	Leu L	Lys K	...
Ala A	13	6	9	9	5	8	9	12	6	8	6	7	...
Arg R	3	17	4	3	2	5	3	2	6	3	2	9	
Asn N	4	4	6	7	2	5	6	4	6	3	2	5	
Asp D	5	4	8	11	1	7	10	5	6	3	2	5	
Cys C	2	1	1	1	52	1	1	2	2	2	1	1	
Gln Q	3	5	5	6	1	10	7	3	7	2	3	5	
...													
Trp W	0	2	0	0	0	0	0	0	1	0	1	0	
Tyr Y	1	1	2	1	3	1	1	1	3	2	2	1	
Val V	7	4	4	4	4	4	4	4	5	4	15	10	

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BLOSUM

- **Blo**cks **Su**bstitution **M**atrix
- Scores derived from *observations* of the frequencies of substitutions in blocks of local alignments in related proteins
- Matrix name indicates evolutionary distance
  - BLOSUM62 was created using sequences sharing no more than 62% identity

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The Blosum50 Scoring Matrix

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V	B	Z	X	*
A	5	-2	-1	-2	-1	-1	-1	0	-2	-1	-2	-1	-1	-3	-1	1	0	-3	-2	0	-2	-1	-1	-5
R	-2	7	-1	-2	-4	1	0	-3	0	-4	-3	3	-2	-3	-3	-1	-1	-3	-1	-3	-1	0	-1	-5
N	-1	-1	7	2	-2	0	0	0	1	-3	-4	0	-2	-4	-2	1	0	-4	-2	-3	4	0	-1	-5
D	-2	-2	2	8	-4	0	2	-1	-1	-4	-4	-1	-4	-5	-1	0	-1	-5	-3	-4	5	1	-1	-5
C	-1	-4	-2	-4	13	-3	-3	-3	-2	-2	-3	-3	-2	-4	-4	-1	-1	-5	-3	-1	-3	-3	-2	-5
Q	-1	1	0	0	-3	7	2	-2	1	-3	-2	2	0	-4	-1	0	-1	-1	-1	-3	0	4	-1	-5
E	-1	0	0	2	-3	2	6	-3	0	-4	-3	1	-2	-3	-1	-1	-1	-3	-2	-3	1	5	-1	-5
G	0	-3	0	-1	-3	-2	-3	8	-2	-4	-4	-2	-3	-4	-2	0	-2	-3	-3	-4	-1	-2	-2	-5
H	-2	0	1	-1	-3	1	0	-2	10	-4	-3	0	-1	-1	-2	-1	-2	-3	2	-4	0	0	-1	-5
I	-1	-4	-3	-4	-2	-3	-4	-4	-4	5	2	-3	2	0	-3	-3	-1	-3	-1	4	-4	-3	-1	-5
L	-2	-3	-4	-4	-2	-2	-3	-4	-3	2	5	-3	3	1	-4	-3	-1	-2	-1	1	-4	-3	-1	-5
K	-1	3	0	-1	-3	2	1	-2	0	-3	-3	6	-2	-4	-1	0	-1	-3	-2	-3	0	1	-1	-5
M	-1	-2	-2	-4	-2	0	-2	-3	-1	2	3	-2	7	0	-3	-2	-1	-1	0	1	-3	-1	-1	-5
F	-3	-3	-4	-5	-2	-4	-3	-4	-1	0	1	-4	0	8	-4	-3	-2	1	4	-1	-4	-4	-2	-5
P	-1	-3	-2	-1	-4	-1	-1	-2	-2	-3	-4	-1	-3	-4	10	-1	-1	-4	-3	-3	-2	-1	-2	-5
S	1	-1	1	0	-1	0	-1	0	-1	-3	-3	0	-2	-3	-1	5	2	-4	-2	-2	0	0	-1	-5
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	2	5	-3	-2	0	0	-1	0	-5
W	-3	-3	-4	-5	-5	-1	-3	-3	-3	-3	-2	-3	-1	1	-4	-4	-3	15	2	-3	-5	-2	-3	-5
Y	-2	-1	-2	-3	-3	-1	-2	-3	2	-1	-1	-2	0	4	-3	-2	-2	2	8	-1	-3	-2	-1	-5
V	0	-3	-3	-4	-1	-3	-3	-4	-4	4	1	-3	1	-1	-3	-2	0	-3	-1	5	-4	-3	-1	-5
B	-2	-1	4	5	-3	0	1	-1	0	-4	-4	0	-3	-4	-2	0	0	-5	-3	-4	5	2	-1	-5
Z	-1	0	0	1	-3	4	5	-2	0	-3	-3	1	-1	-4	-1	0	-1	-2	-2	-3	2	5	-1	-5
X	-1	-1	-1	-1	-2	-1	-1	-1	-1	-1	-1	-1	-1	-2	-2	-1	0	-3	-1	-1	-1	-1	-1	-5
*	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	1

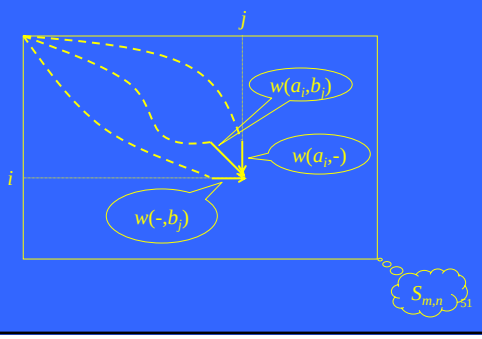
An optimal alignment

-- an alignment of maximum score

- Let A=$a_1a_2\ldots a_m$ and $B=b_1b_2\ldots b_n$.
- $S_{i,j}$: the score of an optimal alignment between $a_1a_2\ldots a_i$ and $b_1b_2\ldots b_j$
- With proper initializations, $S_{i,j}$ can be computed as follows.

$$s_{i,j} = \max\begin{cases} s_{i-1,j} + w(a_i,-) \\ s_{i,j-1} + w(-,b_j) \\ s_{i-1,j-1} + w(a_i,b_j) \end{cases}$$

Computing $S_{i,j}$



Initialization

		C	G	G	A	T	C	A	T
	0	-3	-6	-9	-12	-15	-18	-21	-24
C	-3								
T	-6								
T	-9								
A	-12								
A	-15								
C	-18								
T	-21								

$S_{3,5}$ = ?

		C	G	G	A	T	C	A	T
	0	-3	-6	-9	-12	-15	-18	-21	-24
C	-3	8	5	2	-1	-4	-7	-10	-13
T	-6	5	3	0	-3	7	4	1	-2
T	-9	2	0	-2	-5	?			
A	-12								
A	-15								
C	-18								
T	-21								

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$S_{3,5}$ = ?

		C	G	G	A	T	C	A	T
	0	-3	-6	-9	-12	-15	-18	-21	-24
C	-3	8	5	2	-1	-4	-7	-10	-13
T	-6	5	3	0	-3	7	4	1	-2
T	-9	2	0	-2	-5	5	-1	-4	9
A	-12	-1	-3	-5	6	3	0	7	6
A	-15	-4	-6	-8	3	1	-2	8	5
C	-18	-7	-9	-11	0	-2	9	6	3
T	-21	-10	-12	-14	-3	8	6	4	14

optimal score

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C T T A A C – T
C G G A T C A T
8 – 5 –5 +8 -5 +8 -3 +8 = 14

		C	G	G	A	T	C	A	T
	0	-3	-6	-9	-12	-15	-18	-21	-24
C	-3	8	5	2	-1	-4	-7	-10	-13
T	-6	5	3	0	-3	7	4	1	-2
T	-9	2	0	-2	-5	5	-1	-4	9
A	-12	-1	-3	-5	6	3	0	7	6
A	-15	-4	-6	-8	3	1	-2	8	5
C	-18	-7	-9	-11	0	-2	9	6	3
T	-21	-10	-12	-14	-3	8	6	4	14

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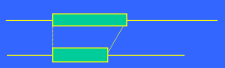
Global Alignment vs. Local Alignment

- global alignment:

- local alignment:



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An optimal local alignment

- $S_{i,j}$: the score of an optimal local alignment ending at a_i and b_j
- With proper initializations, $S_{i,j}$ can be computed as follows.

$$s_{i,j} = \max \begin{cases} 0 \\ s_{i-1,j} + w(a_i, -) \\ s_{i,j-1} + w(-, b_j) \\ s_{i-1,j-1} + w(a_i, b_j) \end{cases}$$

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local alignment

Match: 8
Mismatch: -5
Gap symbol: -3

		C	G	G	A	T	C	A	T
	0	0	0	0	0	0	0	0	0
C	0	8	5	2	0	0	8	5	2
T	0	5	3	0	0	8	5	3	13
T	0	2	0	0	0	8	5	2	11
A	0	0	0	0	8	5	3	?	
A	0								
C	0								
T	0								

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local alignment

Match: 8
Mismatch: -5
Gap symbol: -3

		C	G	G	A	T	C	A	T
	0	0	0	0	0	0	0	0	0
C	0	8	5	2	0	0	8	5	2
T	0	5	3	0	0	8	5	3	13
T	0	2	0	0	0	8	5	2	11
A	0	0	0	0	8	5	3	13	10
A	0	0	0	0	8	5	2	11	8
C	0	8	5	2	5	3	13	10	7
T	0	5	3	0	2	13	10	8	18

the best score

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```
A - C - T
A T C A T
8-3+8-3+8 = 18
```

		C	G	G	A	T	C	A	T
	0	0	0	0	0	0	0	0	0
C	0	8	5	2	0	0	8	5	2
T	0	5	3	0	0	8	5	3	13
T	0	2	0	0	0	8	5	2	11
A	0	0	0	0	8	5	3	13	10
A	0	0	0	0	8	5	2	11	8
C	0	8	5	2	5	3	13	10	7
T	0	5	3	0	2	13	10	8	18

(not always at the corner)

the best score

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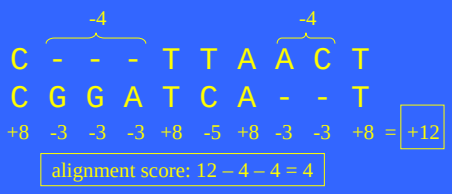
Affine gap penalties

- Match: +8 ($w(x, y) = 8$, if $x = y$)
- Mismatch: -5 ($w(x, y) = -5$, if $x \neq y$)
- Each gap symbol: -3 ($w(-,x)=w(x,-)=-3$)
- *E.g.* each gap is charged an extra gap-open penalty: -4.
- In general, a gap of length k should have penalty $g(k)$



Affine gap penalties

- A gap of length k is penalized $x + k \cdot y$.

gap-open penalty

gap-symbol penalty

Three cases for alignment endings:

1. `...x` / `...x` } an aligned pair
2. `...x` / `...-` } a deletion
3. `...-` / `...x` } an insertion

Affine gap penalties

- Let $D(i, j)$ denote the maximum score of any alignment between $a_1a_2...a_i$ and $b_1b_2...b_j$ ending with a deletion.
- Let $I(i, j)$ denote the maximum score of any alignment between $a_1a_2...a_i$ and $b_1b_2...b_j$ ending with an insertion.
- Let $S(i, j)$ denote the maximum score of any alignment between $a_1a_2...a_i$ and $b_1b_2...b_j$.

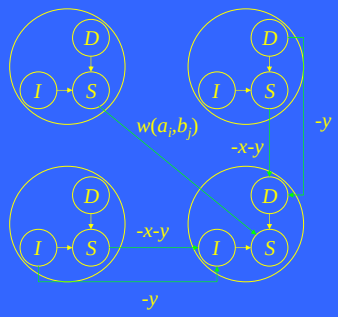
Affine gap penalties

$$D(i, j) = \max\begin{cases} D(i-1, j) - y \\ S(i-1, j) - x - y \end{cases}$$

$$I(i, j) = \max\begin{cases} I(i, j-1) - y \\ S(i, j-1) - x - y \end{cases}$$

$$S(i, j) = \max\begin{cases} S(i-1, j-1) + w(a_i, b_j) \\ D(i, j) \\ I(i, j) \end{cases}$$

Affine gap penalties (Gotoh's algorithm)



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k best local alignments

- Smith-Waterman
  (Smith and Waterman, 1981; Waterman and Eggert, 1987)
- FASTA
  (Wilbur and Lipman, 1983; Lipman and Pearson, 1985)
- BLAST
  (Altschul et al., 1990; Altschul et al., 1997)

BLAST and FASTA are key genomic database search tools.

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k best local alignments

- Smith-Waterman
  (Smith and Waterman, 1981; Waterman and Eggert, 1987)
  - linear-space version：sim (Huang and Miller, 1991)
  - linear-space variants：sim2 (Chao et al., 1995); sim3 (Chao et al., 1997)
- FASTA
  (Wilbur and Lipman, 1983; Lipman and Pearson, 1985)
  - linear-space band alignment (Chao et al., 1992)
- BLAST
  (Altschul et al., 1990; Altschul et al., 1997)
  - restricted affine gap penalties (Chao, 1999)

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FASTA

1) Find runs of identities, and identify regions with the highest density of identities.
2) Re-score using PAM matrix, and keep top scoring segments.
3) Eliminate segments that are unlikely to be part of the alignment.
4) Optimize the alignment in a band.

Its running time is $O(n)$.

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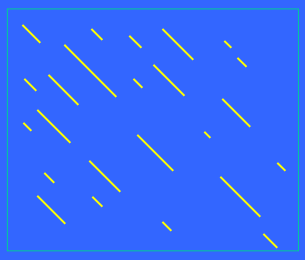
FASTA

Step 1: Find runs of identities, and identify regions with the highest density of identities.



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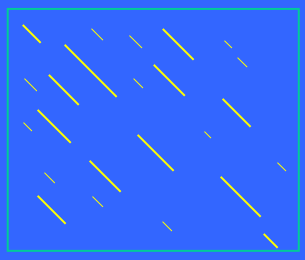
FASTA

Step 2: Re-score using PAM matrix, and keep top scoring segments.



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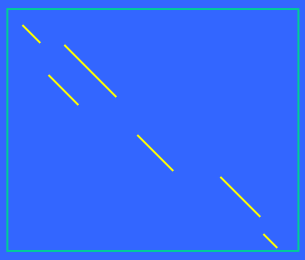
FASTA

Step 3: Eliminate segments that are unlikely to be part of the alignment.



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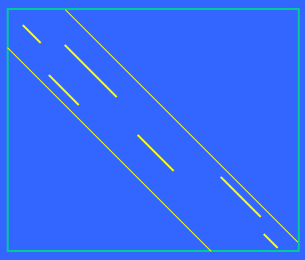
FASTA

Step 4: Optimize the alignment in a band.



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BLAST

1) Build the hash table for sequence A (the database sequence).
2) Scan sequence B for hits.
3) Extend hits.

Also O(n) time.

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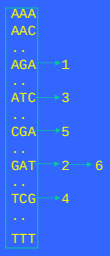
BLAST

Step 1: Build the hash table for sequence A. (3-tuple example)

For DNA sequences:

```
Seq. A = AGATCGAT
         12345678
```



For protein sequences:

```
Seq. A = ELVIS
```

Add *xyz* to the hash table if *Score(xyz, ELV)* $\geqq T$;
Add *xyz* to the hash table if *Score(xyz, LVI)* $\geqq T$;
Add *xyz* to the hash table if *Score(xyz, VIS)* $\geqq T$;

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BLAST

Step2: Scan sequence B for hits.

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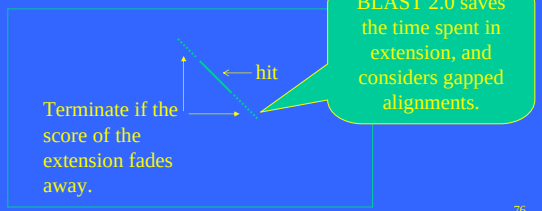
BLAST

Step2: Scan sequence B for hits.

Step 3: Extend hits.



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Remarks

- Filtering is based on the observation that a good alignment usually includes short identical or very similar fragments.
- The idea of filtration was used in both FASTA and BLAST to achieve high speed

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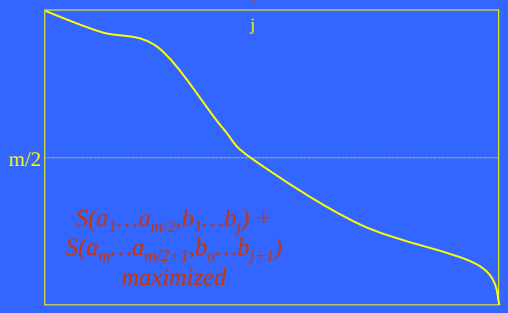
Linear space ideas

Hirschberg, 1975; Myers and Miller, 1988

(i) scores can be computed in $O(n)$ space

(ii) divide-and-conquer



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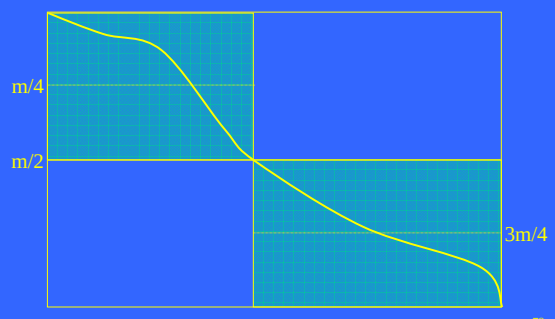
Two subproblems

½ original problem size



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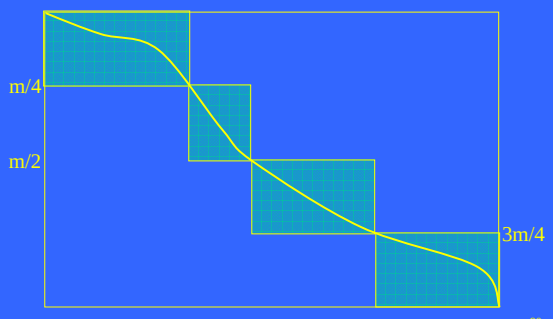
Four subproblems

¼ original problem size



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Time and Space Complexity

- Space: $O(m+n)$
- Time:

$$O(mn)*(\underbrace{1+ \tfrac{1}{2} + \tfrac{1}{4} + \ldots}_{2}) = O(mn)$$

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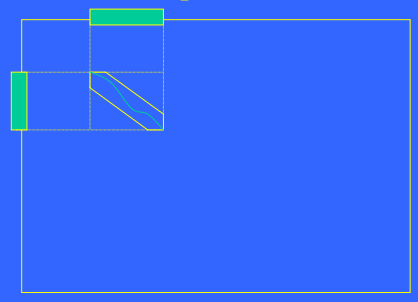
Band Alignment

(K. Chao, W. Pearson, and W. Miller)

Sequence A



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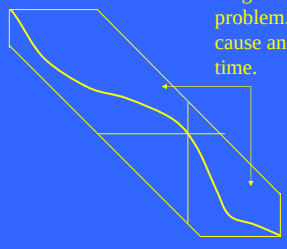
Band Alignment in Linear Space



The remaining subproblems are no longer only half of the original problem. In worst case, this could cause an additional log *n* factor in time.

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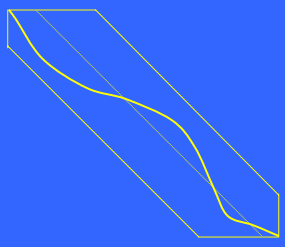
Band Alignment in Linear Space



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Multiple sequence alignment (MSA)

- The multiple sequence alignment problem is to simultaneously align more than two sequences.

```
Seq1: GCTC      GC-TC
Seq2: AC        A---C
Seq3: GATC      G-ATC
```

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How to score an MSA?

- *Sum-of-Pairs* (SP-score)

$$\text{Score}\begin{pmatrix}\texttt{GC-TC}\\ \texttt{A---C}\\ \texttt{G-ATC}\end{pmatrix} = \text{Score}\begin{pmatrix}\texttt{GC-TC}\\ \texttt{A---C}\end{pmatrix} + \text{Score}\begin{pmatrix}\texttt{GC-TC}\\ \texttt{G-ATC}\end{pmatrix} + \text{Score}\begin{pmatrix}\texttt{A---C}\\ \texttt{G-ATC}\end{pmatrix}$$

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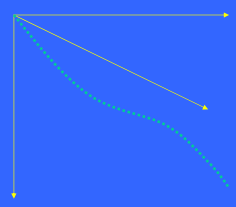
MSA for three sequences

- an $O(n^3)$ algorithm



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General MSA

- For k sequences of length n: $O(n^k)$
- NP-Complete (Wang and Jiang)
- The exact multiple alignment algorithms for many sequences are not feasible.
- Some approximation algorithms are given. (*e.g.*, 2- *l*/*k* for any fixed *l* by Bafna *et al.*)

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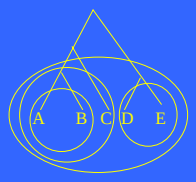
Progressive alignment

- A heuristic approach proposed by Feng and Doolittle.
- It iteratively merges the most similar pairs.
- "Once a gap, always a gap"



The time for progressive alignment in most cases is roughly the order of the time for computing all pairwise alignment, i.e., $O(k^2n^2)$.

Concluding remarks

- Three essential components of the dynamic programming approach:
  - the recurrence relation
  - the tabular computation
  - the backtracing
- The dynamic-programming approach has been used in a vast number of computational problems in bioinformatics.