Pairwise Sequence Alignment (II)

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Pairwise Alignment Algorithm Using Dynamic Programming

- Initialization: Given two sequences with length m and n, create a (m+1)×(n+1) matrix M. Initialize the first row and first column according to scoring matrix.
- For j in 1..n (column)

  for i in 1..m (row)

  M[i,j] = max((M[i-1,j-1]+S(i,j), M[i,j-1]+S(-,j), M[i-1, j] + S(i,-))

  Record the selected path toward (i,j)
- Report alignment score M[m][n] and trace back to M[0,0] to generate the optimal alignment.

Local Sequence Alignment Using DP

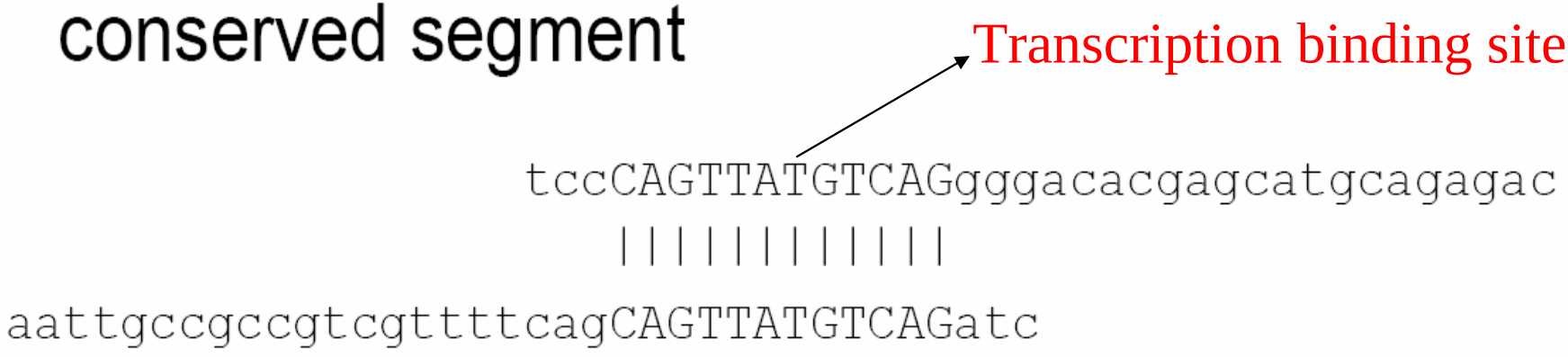
- Biological sequences usually only have local similarity. For instance: a protein sequence may consist of a few modules. Two proteins may only have one similar modules, whereas other regions are not similar at all.
- During evolution, only functional and structural important regions are highly conserved.
- Global alignment sacrifices the local similarity to maximize the global alignment score.
- We need to use alignment method to identify the local similar regions disregard of other dissimilar regions.

Local vs. Global Alignment

- Global Alignment

```
--T--CC-C-AGT--TATGT-CAGGGGACACG-A-GCATGCAGA-GAC
  |   || |   ||   | | | |||     || | | |   | ||||    |
AATTGCCGCC-GTCGT-T-TTCAG----CA-GTTATG-T-CAGAT--C
```

- Local Alignment—better alignment to find conserved segment



Local Alignment Algorithm

Goal: find an alignment of the substrings of P and Q with maximum alignment score.

Naïve Algorithm:

(m+1)*m/2 substrings of P, (n+1)*n/2 substrings of Q

Using DP for each substring pairs:

m^2 * n^2 * O(mn) = O(m^3n^3)

(too slow!)

Smith-Waterman Algorithm

Same Dynamic Program algorithm as global alignment except for three differences.

1. All negative scores is converted to 0 (why?)
2. Alignment can start from anywhere in the matrix
3. Alignment can end at anywhere in the matrix

Local Alignment Algorithm

- Initialization: Given two sequences with length m and n, create a (m+1)×(n+1) matrix M. Initialize the first row and first column to 0s.
- For j in 1..n (column)

  for i in 1..m (row)

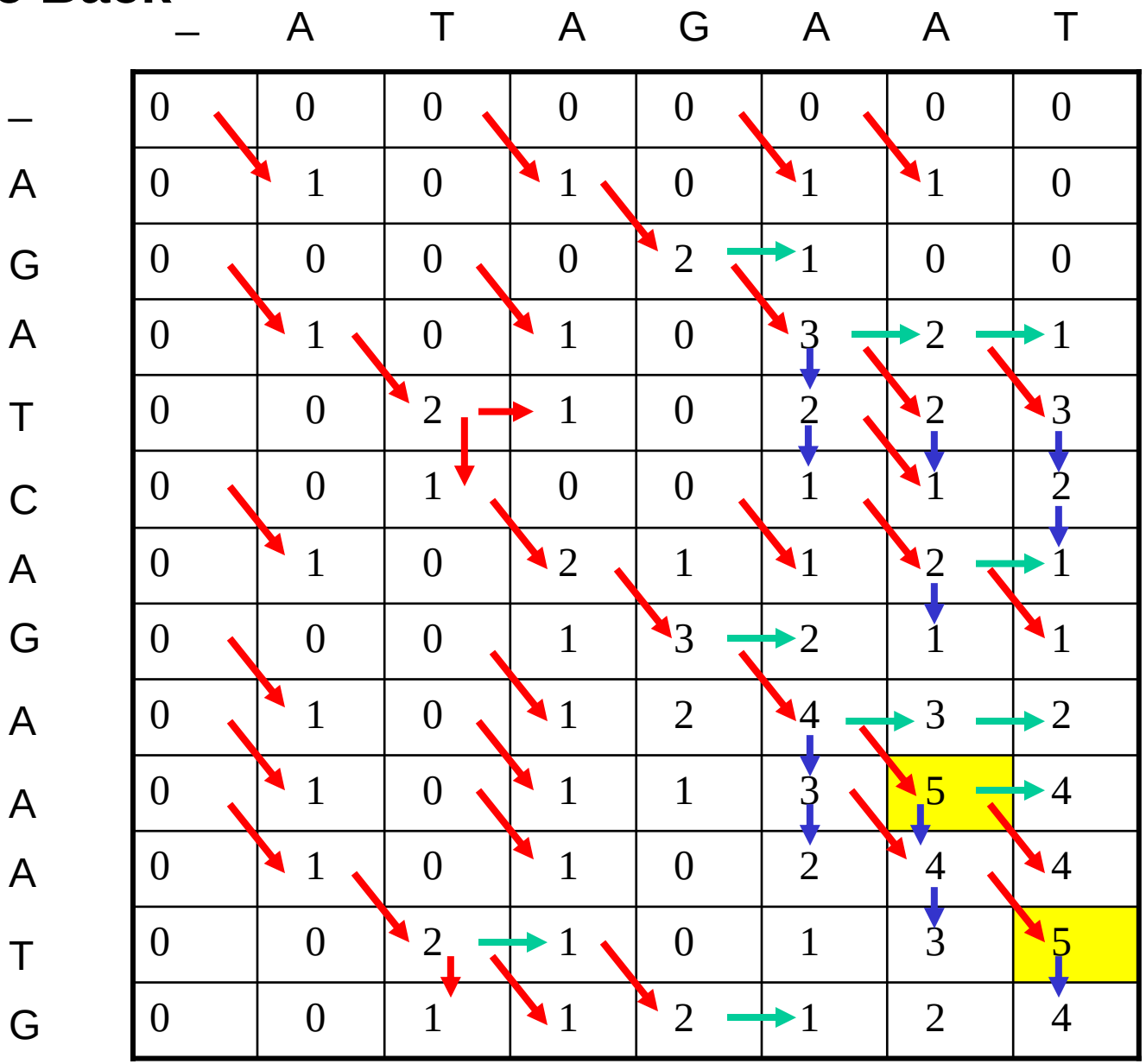
  M[i,j] = max(0, (M[i-1,j-1]+S(i,j), M[i,j-1]+S(-,j), M[i-1, j] + S(i,-))

  Record the selected path.
- Find elements in matrix M with maximum values. Trace back till 0 and report the alignment corresponding to the path.

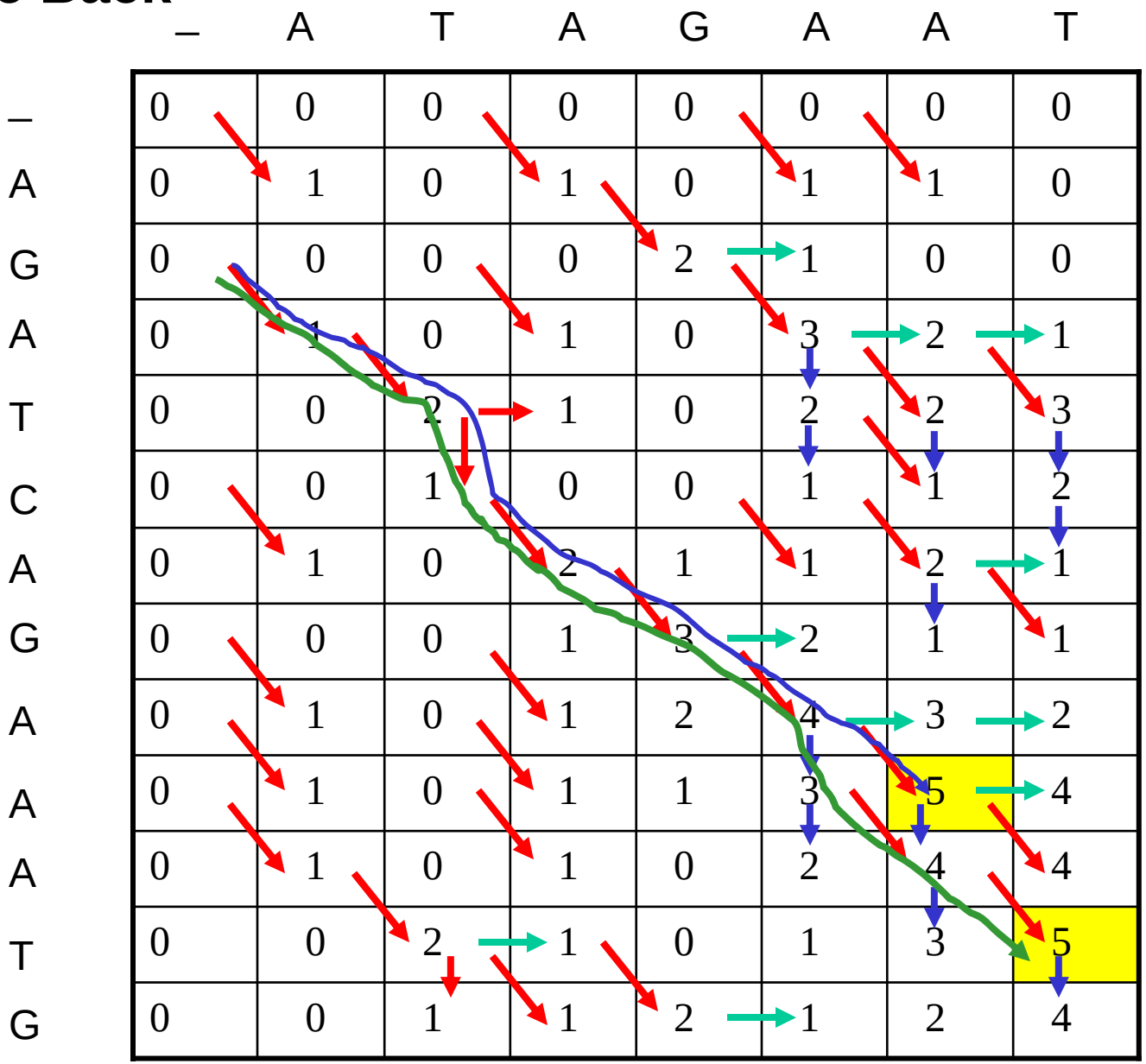
1. Initialization

	–	A	T	A	G	A	A	T
–	0	0	0	0	0	0	0	0
A	0							
G	0							
A	0							
T	0							
C	0							
A	0							
G	0							
A	0							
A	0							
A	0							
T	0							
G	0							

3. Trace Back


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

3. Trace Back


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

Two Best Local Alignments

Local Alignment 1:

```
ATCAGAA
AT-AGAA
```

Local Alignment 2:

```
ATCAGAAAT
AT-AGA-AT
```

Affine Gap Penalty

- We have treated gaps independently. However, gaps in biological sequences are dependent.
- Hard to open the first gap, and easy to extend gaps.
- First gap should be penalized more than extended gaps.

Affine Gap Function

- Penalty of gaps = Wo + We * (g-1)
- Wo: penalty of opening a gap
- We: penalty of extending a gap
- g: gap size
- Example: Wo = -2, We = -1

Example:

AGATCAGAAATG

--AT-AG-AAT-

Alignment score: -2 -1 +1 +1 – 2 +1 +1 -2 +1 +1 + 1 -2 = -2

Complexity of Affine Gap Penalty

- To compute the alignment score, we need to know the state of the previous alignment:

  last pair matches two characters?

  last pair matches P[k] with a gap?

  last pair matches Q[t] with a gap?

So we need to introduce more matrices to record the scores in these three situations.

Dynamic programming with Affine Gap Penalty

- Algorithms proceeds by aligning P[1..i] with Q[1..j]. For these prefixes of P and Q, define the following four matrices V, G, F, E:
- V[i,j] is the value of an optimal alignment of prefix P[1..i] and prefix Q[1..j].
- G[i,j] is the value of an optimal alignment of P[1..i] and Q[1..j] whose last pair matches P[i] with Q[j]
- F(i,j) is the value of an optimal alignment of P[1..i] and T[1..j] whose last pair matches P[i] with a gap.
- E(i,j) is the value of an optimal alignment of P[1..i] and Q[1..j] whose last pair matches a gap with Q[j]

Initialization

- $V(0,0) = 0$
- $V(i,0) = Wo + We * (i - 1)$
- $V(0,j) = Wo + We * (j-1)$
- $E(i,0) = -\infty$
- $F(0,j) = -\infty$

Fill Matrix

- V(i,j) = max (G(i,j), F(i,j), E(i,j))
- G(i,j) = V(i-1, j-1) + S(P[i], Q[j])
- F(i,j) = max(F(i-1,j)+We, G(i-1,j) + Wo, E(i-1, j) + Wo
- E(i,j) = max(E(i,j-1) + We, G(i,j-1) + Wo, F(i,j-1) + Wo)

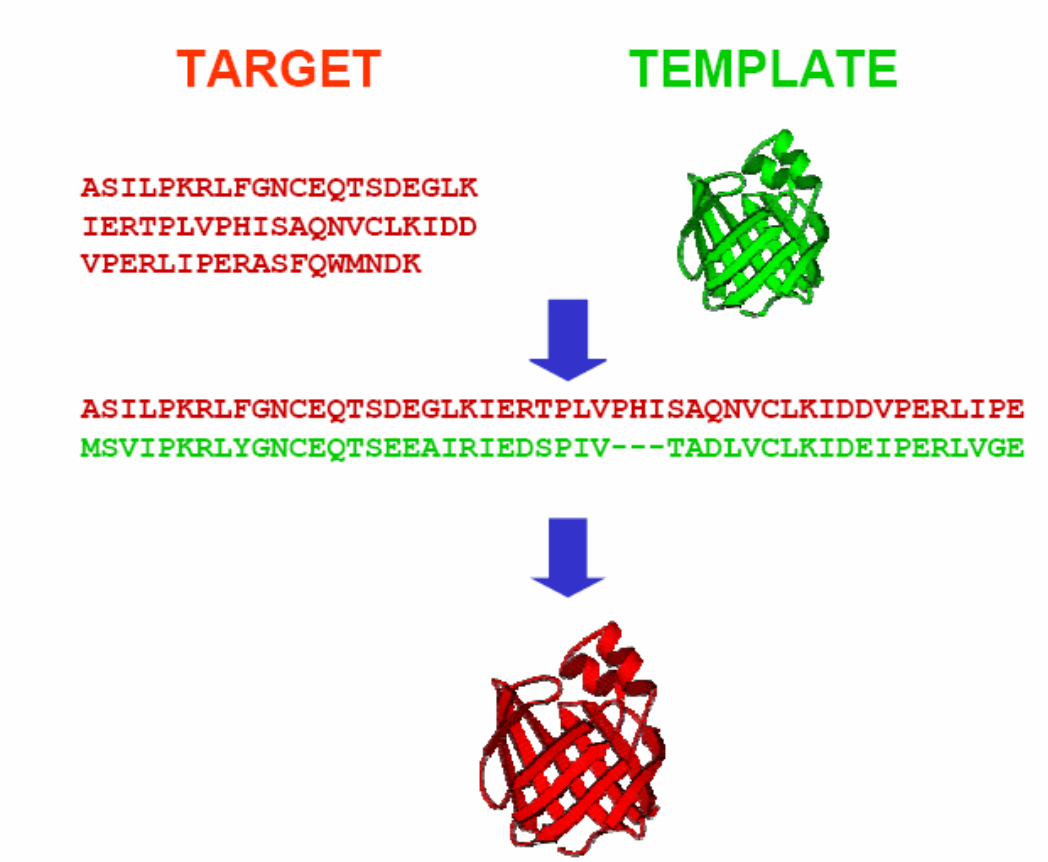
Trace Back

- Trace within matrix and across matrices
- Time and space complexity: O(m*n)
- Comments: four matrices. 3 matrices for three different possible ending states. 1 matrix is the master matrix to record the best alignment scores from those three matrices.

Comments

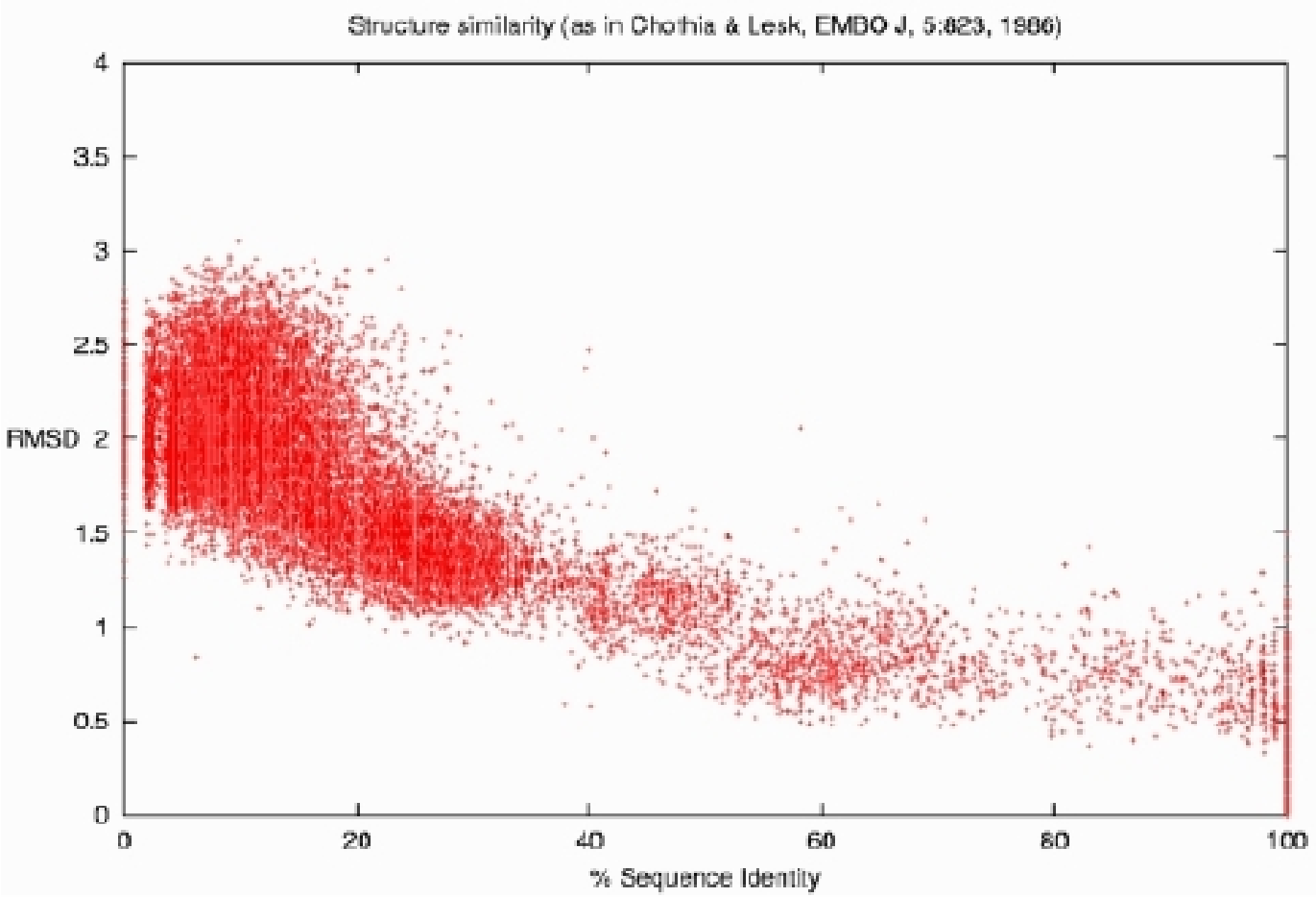
- Does sequence alignment based on mathematical optimization really make biological sense?
- When alignment is good?
- When alignment is bad?
- Alignment quality and sequence identity relationship

Application Example (Alignment – Structure)



Source: A. Fisher, 2005

Sequence Identity and Alignment Quality in Structure Prediction



Superimpose
-> RMSD

%Sequence Identity: percent of identical residues in alignment
RMSD: square root of average distance between predicted structure and native structure.

Global and Local Alignment Tools

- NEEDLE (global alignment)

  http://bioweb.pasteur.fr/seqanal/interfaces/needle.html

- WATER (local alignment)

  http://bioweb.pasteur.fr/seqanal/interfaces/water.html