Dynamic Programming and Applications

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Bioinformatics Lecture 2
Quantitative Biology 2014

Exact Matching Review

Where is GATTACA in the human genome?
E=183,105

Brute Force (3 GB)	Suffix Array (>15 GB)	BWT/FM-Index (~ 3GB)
BANANA BAN ANA NAN ANA	6 $ 5 A$ 3 ANA$ 1 ANANA$ 0 BANANA$ 4 NA$ 2 NANA$	$BANAN**A** A$BANA**N** ANA$BA**N** ANANA$**B** BANANA**$** NA$BAN**A** NANA$B**A**
Naive	Vmatch, PacBio Aligner	Bowtie/BWA/SGA
Slow & Easy	Binary Search	Indexed Searching

These are general techniques useful for ***any*** search problem

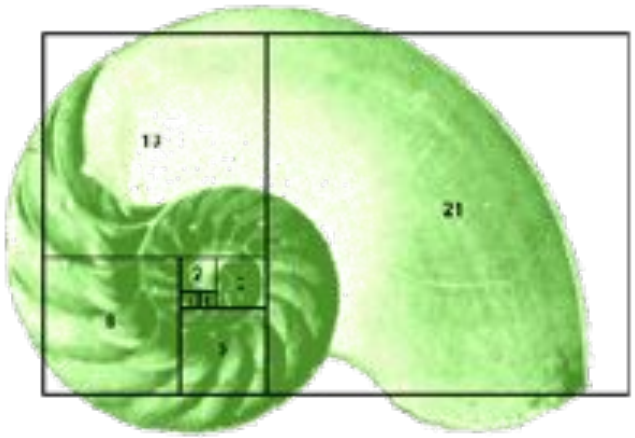
Agenda

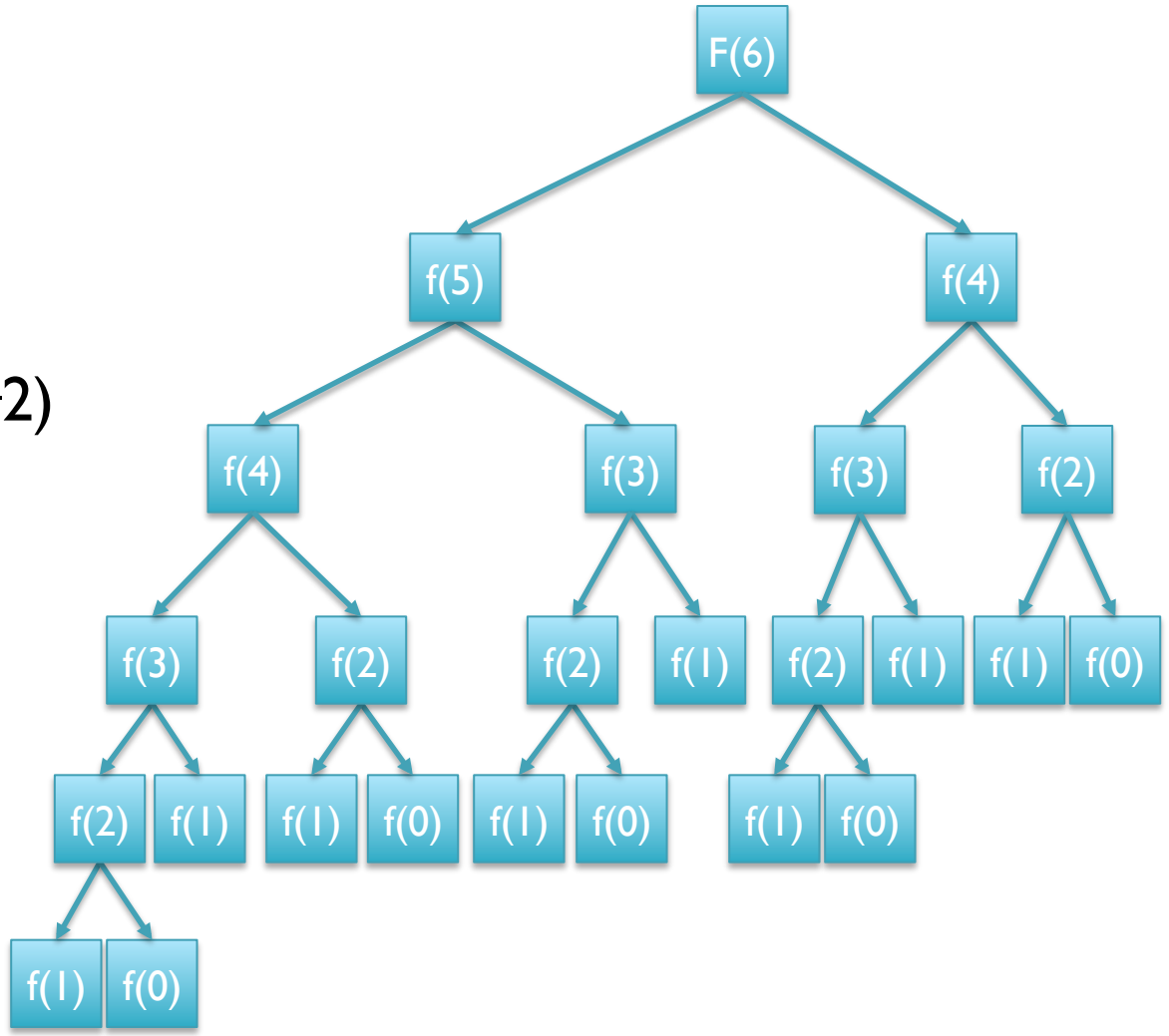
1. Background on Dynamic Programming
    1. Fibonacci Sequences
    2. Longest-Increasing-Subsequences
2. Edit Distance & Alignment
    1. Computing Edit Distances
    2. Global vs Local Alignment
3. Applications
    1. Dynamic Time Warping
    2. BLAST

First:
A quick warm-up exercise

Fibonacci Sequence

```
def fib(n):
  if n == 0 or n == 1:
     return n
  else:
  return fib(n−1) + fib(n−2)
```





Fibonacci Sequence

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def fib(n):
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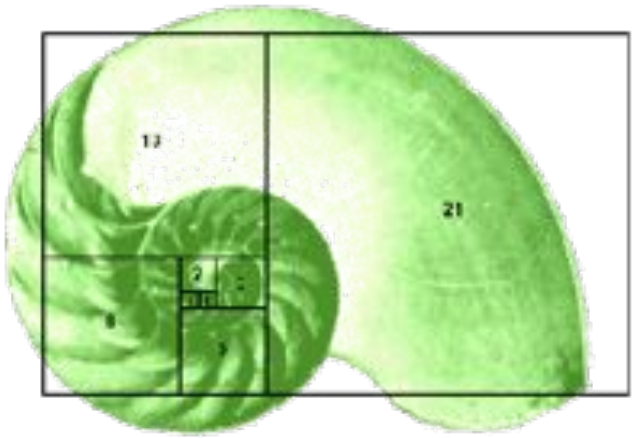
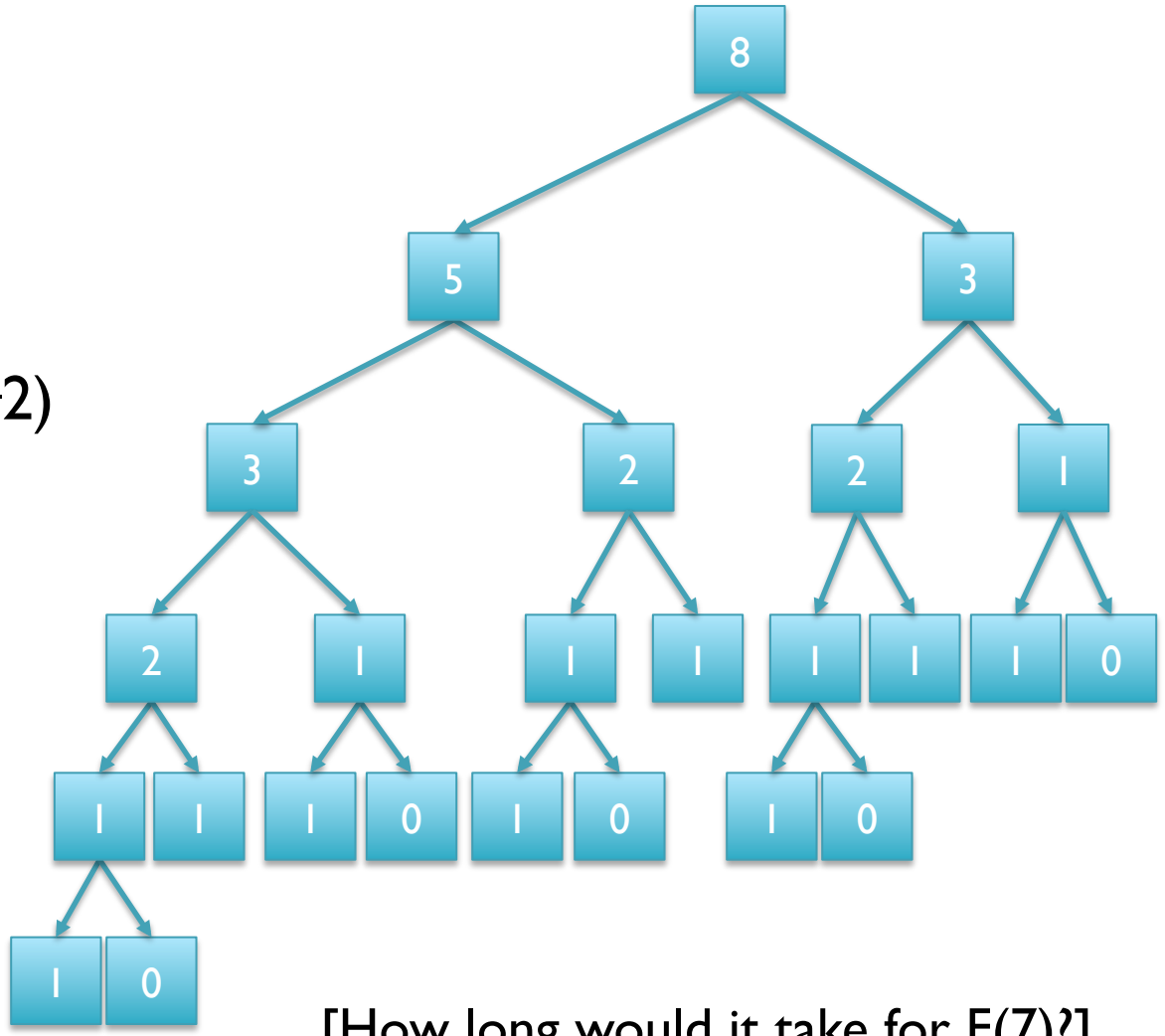


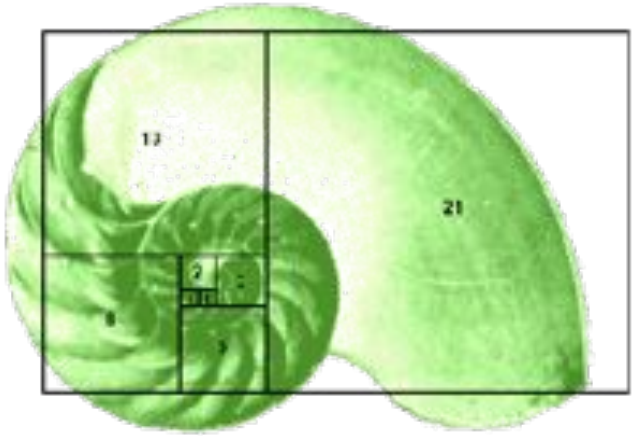


[How long would it take for F(7)?]
[What is the running time?]

Bottom-up Fibonacci Sequence

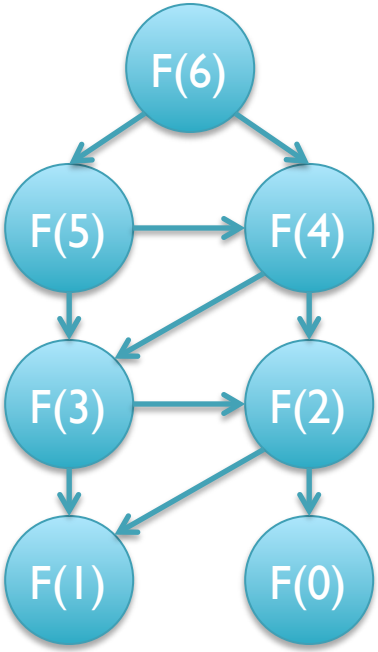
```
def fib(n):
  table = [0] * (n+1)
  table[0] = 0
  table[1] = 1
  for i in range(2,n+1):
    table[i] = table[i−2] + table[i−1]
return table[n]
```

[How long will it take for F(7)?]
[What is the running time?]



Dynamic Programming

- General approach for solving (some) complex problems
  - When applicable, the method takes far less time than naive methods.
    - Polynomial time (O(n) or $O(n^2)$ instead of exponential time ($O(2^n)$ or $O(3^n)$)
- Requirements:
  - **Overlapping subproblems**
  - **Optimal substructure**
- Applications:
  - Fibonacci
  - Longest Increasing Subsequence
  - Sequence alignment, Dynamic Time Warp, Viterbi



- Not applicable:
  - Traveling salesman problem, Clique finding, Subgraph isomorphism, …
  - The cheapest flight from airport A to airport B involves a single connection through airport C, but the cheapest flight from airport A to airport C involves a connection through some other airport D.

Second:
A quick interesting side problem

Longest Increasing Subsequence

- Given a sequence of N numbers A_1, A_2, A_3, … A_N, find the longest monotonically increasing subsequence
  - 29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19
- Greedy approach (always extend the subsequence if you can):
  - 29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19 => 4
- Brute force:
  - Try all possible $O(2^n)$ subsequences

    29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19 => 1

    29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19 => invalid

    29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19 => invalid

    29, 6, 14, 31, 39, 78, 63, 50, 13, 64, 61, 19 => 2

    …

Longest Increasing Subsequence

- Idea:
  - The solution for all N numbers depends on the solution for the first N-1
  - Look through the previous values to find the longest subsequence ending at X such that $A_X < A_N$
- Dynamic Programming:
  - Def: L[j] is the longest increasing subsequence ending at position j
  - Base case: L[0] = 0 Recurrence: $L[j] = \max_{\substack{i<j \\ A[i]<A[j]}} \{L[i]\} + 1$ LIS=max{L[i]}

Index	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Value	-	29	6	14	31	39	78	63	50	13	64	61	62	19
LIS	0	1	1	2	3	4	5	5	5	2	6	6	7	3
Prev	-	0	0	2	3	4	5	5	5	2	5	8	11	3

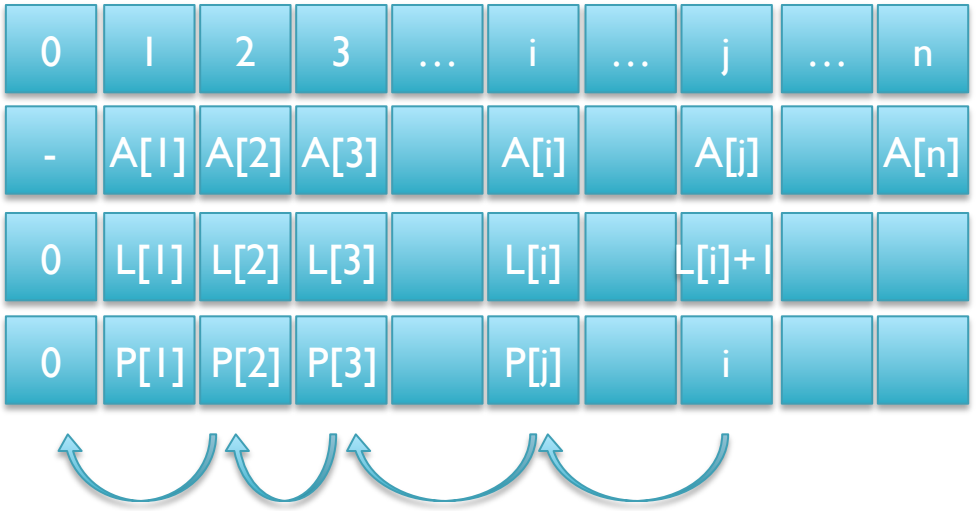
[What's the LIS of 0,8,4,12,2,10,6,14,1,9,5,13,3,11,7,15 ?]

Longest Increasing Subsequence

```
// Initialize
L[0] = 0; P[0] = 0

// Iteratively apply recurrence
for i = 1 to N
      // find the best LIS to extend
      bestlis = 0; bestidx = -1
      for j = 1 to i
            if ((A[j] <= A[i])) && (L[j] > bestlis))
                  bestlis = L[j]; bestidx = j
      L[i] = bestlis + 1;  P[i] = bestidx

// Scan the L array to find the overall LIS
LIS = 0
for j = 1 to N
      if (L[j] > LIS) LIS = L[j]
print "The LIS is $LIS"
```



[What's the running time?]

And now for the main event!

In-exact alignment

- Where is GATTACA *approximately* in the human genome?
  - And how do we efficiently find them?

- It depends…
  - Define 'approximately'
    - Hamming Distance, Edit distance, or Sequence Similarity
    - Ungapped vs Gapped vs Affine Gaps
    - Global vs Local
    - All positions or the single 'best'?
  - Efficiency depends on the data characteristics & goals
    - Bowtie: BWT alignment for short read mapping
    - Smith-Waterman: Exhaustive search for optimal alignments
    - BLAST: Hash based homology searches
    - MUMmer: Suffix Tree based whole genome alignment

Similarity metrics

- Hamming distance
  - Count the number of substitutions to transform one string into another

```
GATTACA        ATTACCC
|||x|||        xx|xx|x
GATCACA        GATTACA
   1              5
```

- Edit distance
  - The minimum number of substitutions, insertions, or deletions to transform one string into another

```
GATTACA        -ATTACCC
|||x|||        x|||||xx
GATCACA        GATTAC-A
   1              3
```

Edit Distance Example

AGCACACA → ACACACTA in 4 steps

AGCACACA → (1. change G to C)
ACCACACA → (2. delete C)
ACACACA → (3. change A to T)
ACACACT → (4. insert A after T)
ACACACTA → done

[Is this the best we can do?]

Edit Distance Example

AGCACACA → ACACACTA in 3 steps

AGCACACA → (1. change G to C)
ACCACACA → (2. delete C)
ACACACA → (3. insert T after 3rd C)
ACACACTA → done

[Is this the best we can do?]

Reverse Engineering Edit Distance

`D(AGCACACA, ACACACTA) = ?`

Imagine we already have the optimal alignment of the strings, the last column can only be 1 of 3 options:

…**M**	…**I**	…**D**
…A	…-	…A
…A	…A	…-

The optimal alignment of last two columns is then 1 of 9 possibilities

…**MM**	…**IM**	…**DM**	…**MI**	…**II**	…**DI**	…**MD**	…**ID**	…**DD**
…CA	…-A	…CA	…A-	…--	…A-	…CA	…-A	…CA
…TA	…TA	…-A	…TA	…TA	…-A	…A-	…A-	…--

The optimal alignment of the last three columns is then 1 of 27 possibilities…

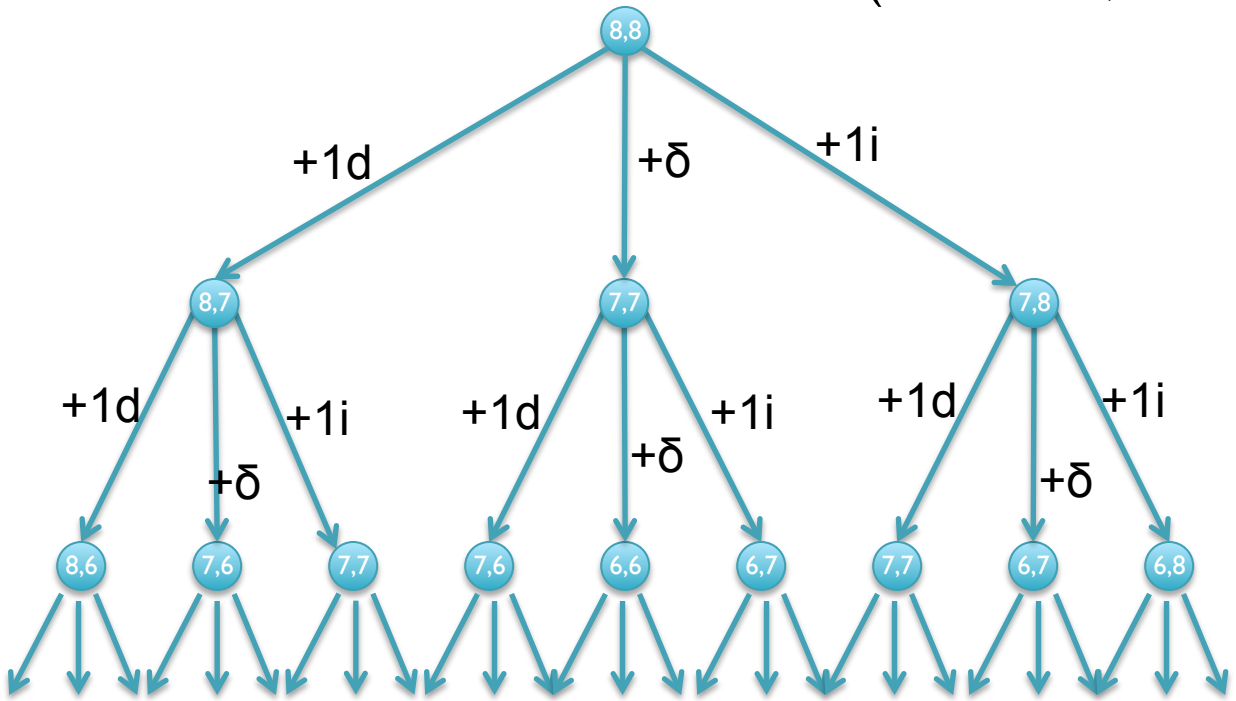
…**M**…	…**I**…	…**D**…
…X…	…-…	…X…
…Y…	…Y…	…-…

Eventually spell out every possible sequence of {I,M,D}

Recursive solution

- Computation of D is a recursive process.
  - At each step, we only allow matches, substitutions, and indels
  - D(i,j) in terms of D(i', j') for i' ≤ i and j' ≤ j.

D(AGCACACA, ACACACTA) = min{D(AGCACACA, ACACACT) + 1,
D(AGCACAC, ACACACTA) + 1,
D(AGCACAC, ACACACT) +δ(A, A)}



[What is the running time?]

Dynamic Programming

- We could code this as a recursive function call...

  ...with an exponential number of function evaluations

- There are only (n+1)x(m+1) pairs i and j
  - We are evaluating D(i,j) multiple times

- Compute D(i,j) bottom up.
  - Start with smallest (i,j) = (1,1).
  - Store the intermediate results in a table.
    - Compute D(i,j) *after* D(i-1,j), D(i,j-1), and D(i-1,j-1)

Recurrence Relation for D

Find the edit distance (minimum number of operations to convert one string into another) in O(mn) time

- Base conditions:
  - D(i,0) = i, for all i = 0,...,n
  - D(0,j) = j, for all j = 0,...,m

- For i > 0, j > 0:

D(i,j) = min {

D(i-1,j) + 1, // align 0 chars from S, 1 from T

D(i,j-1) + 1, // align 1 chars from S, 0 from T

D(i-1,j-1) + δ(S(i),T(j)) // align 1+1 chars

}

[Why do we want the min?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1								
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

[What does the initialization mean?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0							
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

$$D[A,A] = \min\{D[A,]+1,\ D[,A]+1,\ D[,]+\delta(A,A)\}$$

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1						
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

$$D[A,AC] = \min\{D[A,A]+1,\ D[,AC]+1,\ D[,A]+\delta(A,C)\}$$

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2					
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

$$D[A,ACA] = \min\{D[A,AC]+1,\ D[,ACA]+1,\ D[,AC]+\delta(A,A)\}$$

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

D[A,ACACACTA] = 7

```
-------A
*******|
ACACACTA
```

[What about the other A?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2	1	1	2	3	4	5	6	7
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

D[AG,ACACACTA] = 7

```
----AG--
****|***
ACACACTA
```

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2	1	1	2	3	4	5	6	7
C	3	2	1	2	2	3	4	5	6
A	4	3	2	1	2	2	3	4	5
C	5	4	3	2	1	2	2	3	4
A	6	5	4	3	2	1	2	3	3
C	7	6	5	4	3	2	1	2	3
A	8	7	6	5	4	3	2	2	2

D[AGCACACA,ACACACTA] = 2

```
AGCACAC-A
|*|||||*|
A-CACACTA
```

[Can we do it any better?]

Break

Dynamic Programming Matrix

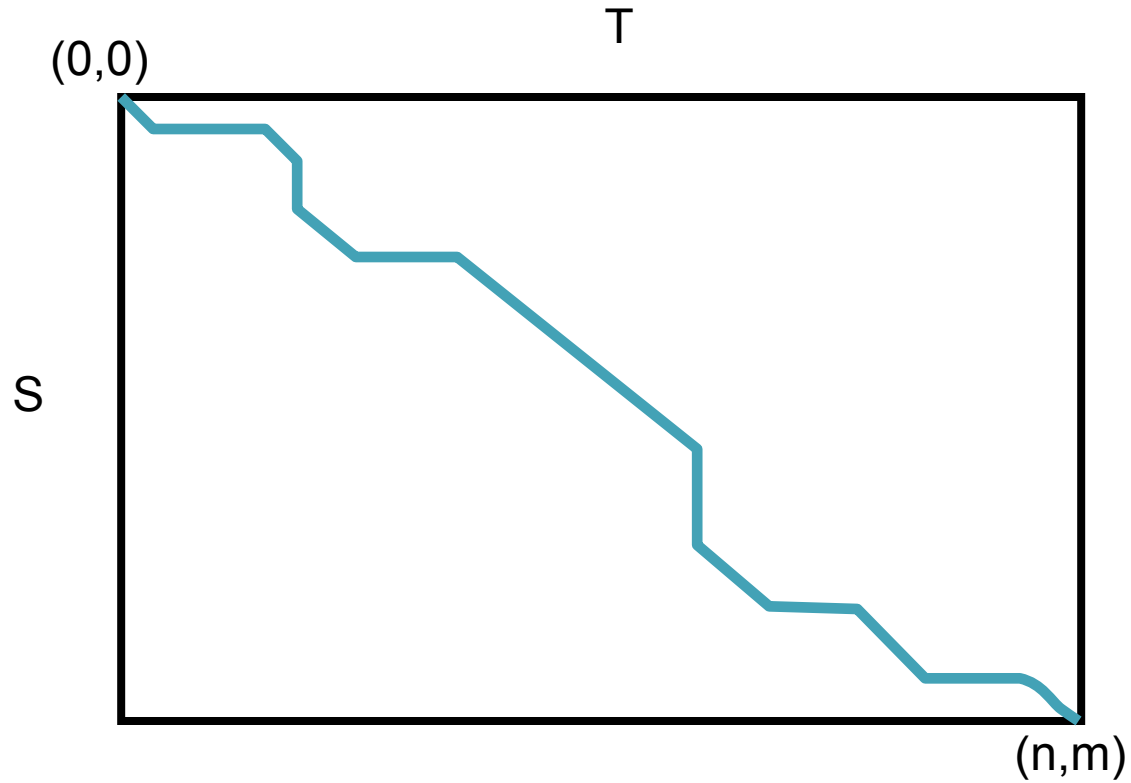
		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2	1	1	2	3	4	5	6	7
C	3	2	1	2	2	3	4	5	6
A	4	3	2	1	2	2	3	4	5
C	5	4	3	2	1	2	2	3	4
A	6	5	4	3	2	1	2	3	3
C	7	6	5	4	3	2	1	2	3
A	8	7	6	5	4	3	2	2	2

D[AGCACACA,ACACACTA] = 2

```
AGCACAC-A
|*|||||*|
A-CACACTA
```

[Can we do it any better?]

Global Alignment Schematic



- A high quality alignment will stay close to the diagonal
  - If we are only interested in high quality alignments, we can skip filling in cells that can't possibly lead to a high quality alignment
  - Find the global alignment with at most edit distance d: O(2dn)

Sequence Similarity

- Similarity score generalizes edit distance
  - Certain mutations are much more likely than others
    - Hydrophilic -> Hydrophillic much more likely than Hydrophillic -> Hydrophobic
  - BLOSSUM62
    - Empirically measure substitution rates among proteins that are 62% identical
    - Positive score: more likely than chance, Negative score: less likely

	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Ala	4																			
Arg	-1	5																		
Asn	-2	0	6																	
Asp	-2	-2	1	6																
Cys	0	-3	-3	-3	9															
Gln	-1	1	0	0	-3	5														
Glu	-1	0	0	2	-4	2	5													
Gly	0	-2	0	-1	-3	-2	-2	6												
His	-2	0	1	-1	-3	0	0	-2	8											
Ile	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
Leu	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
Lys	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
Met	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
Phe	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
Pro	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
Ser	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
Thr	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
Trp	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Tyr	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
Val	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

Edit Distance and Global Similarity

$$D(i,j) = \min \{ D(i-1,j) + 1,\ D(i,j-1) + 1,\ D(i-1,j-1) + \delta(S(i),T(j)) \}$$

s = 4x4 or 20x20 scoring matrix

$$S(i,j) = \max \{ S(i-1,j) - 1,\ S(i,j-1) - 1,\ S(i-1,j-1) + s(S(i),T(j)) \}$$

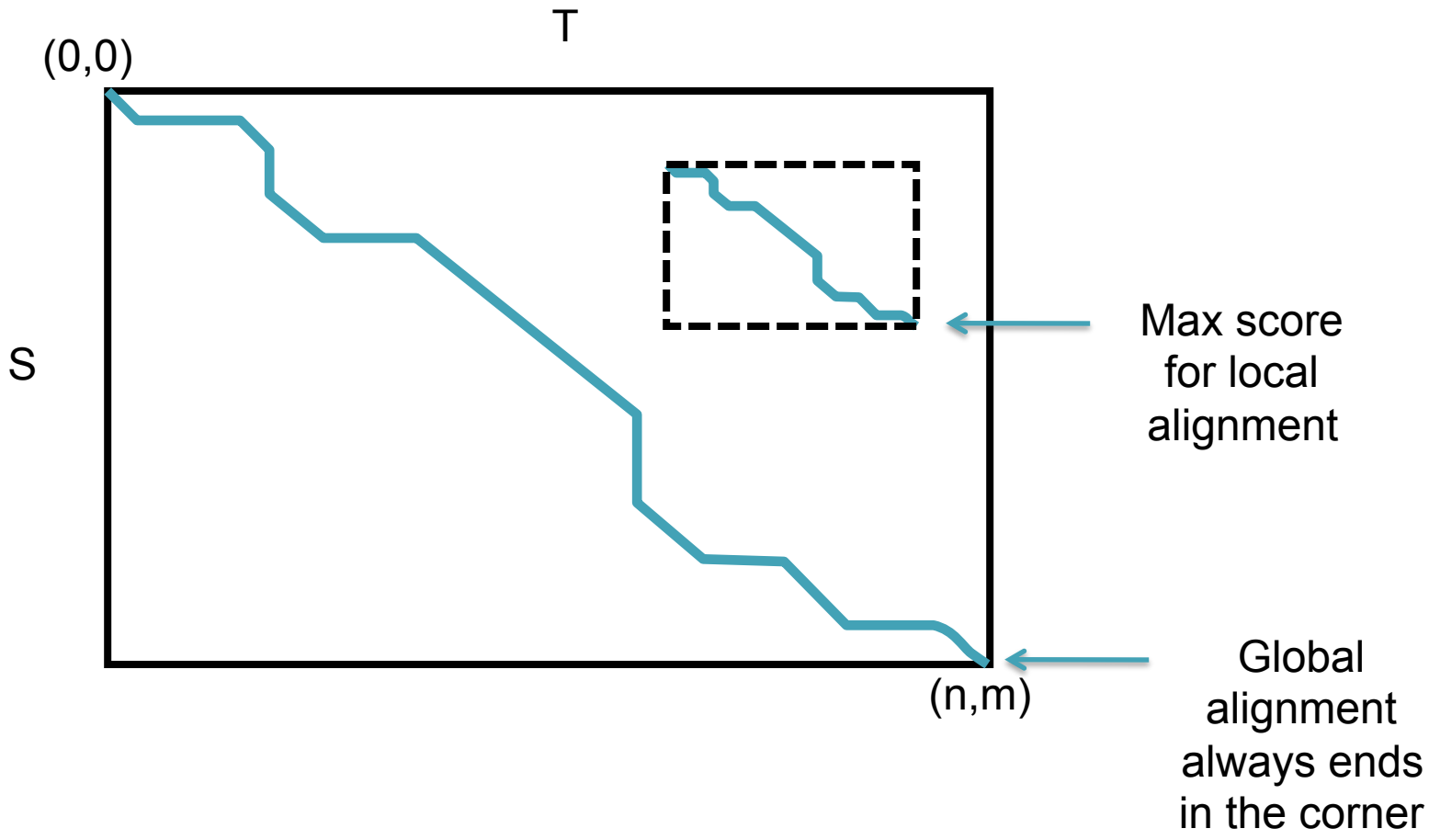
[Why max?]

Local vs. Global Alignment

- The Global Alignment Problem tries to find the best end-to-end alignment between the two strings
  - Only applicable for very closely related sequences

- The Local Alignment Problem tries to find pairs of **substrings** with highest similarity.
  - Especially important if one string is substantially longer than the other
  - Especially important if there is only a distant evolutionary relationship

Global vs Local Alignment Schematic



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Local vs. Global Alignment (cont' d)

- 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

```
                    tccCAGTTATGTCAGgggacacgagcatgcagagac
                       ||||||||||||
aattgccgccgtcgttttcagCAGTTATGTCAGatc
```

The Local Alignment Recurrence

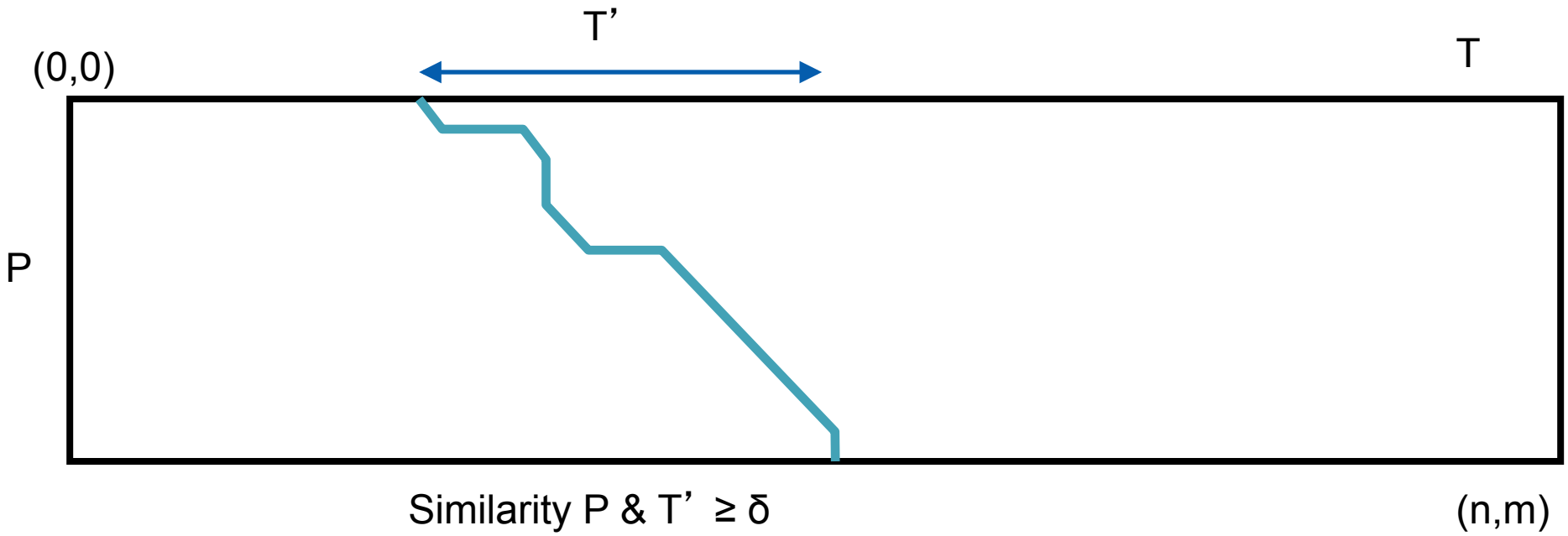
- The largest value of $s_{i,j}$ over the whole edit graph is the score of the best local alignment.

- The recurrence:

$$s_{i,j} = max \begin{cases} 0 \\ s_{i-1,j-1} + \delta(v_i, w_j) \\ s_{i-1,j} + \delta(v_i, -) \\ s_{i,j-1} + \delta(-, w_j) \end{cases}$$

Power of ZERO: there is only this change from the original recurrence of a Global Alignment - since there is only one "free ride" edge entering into every vertex

G-Local Alignments:
Searching for GATTACA



- Don't "charge" for optimal alignment starting in cells (0,j)
  - Base conds: $D(0,j) = 0$, $D(i,0) = \Sigma_{k \le i} s(S(k), \text{'-'})$
- Don't "charge" for ending alignment at end of P (but not necc. T)
  - Find cell (n,j) with edit distance ≤ δ

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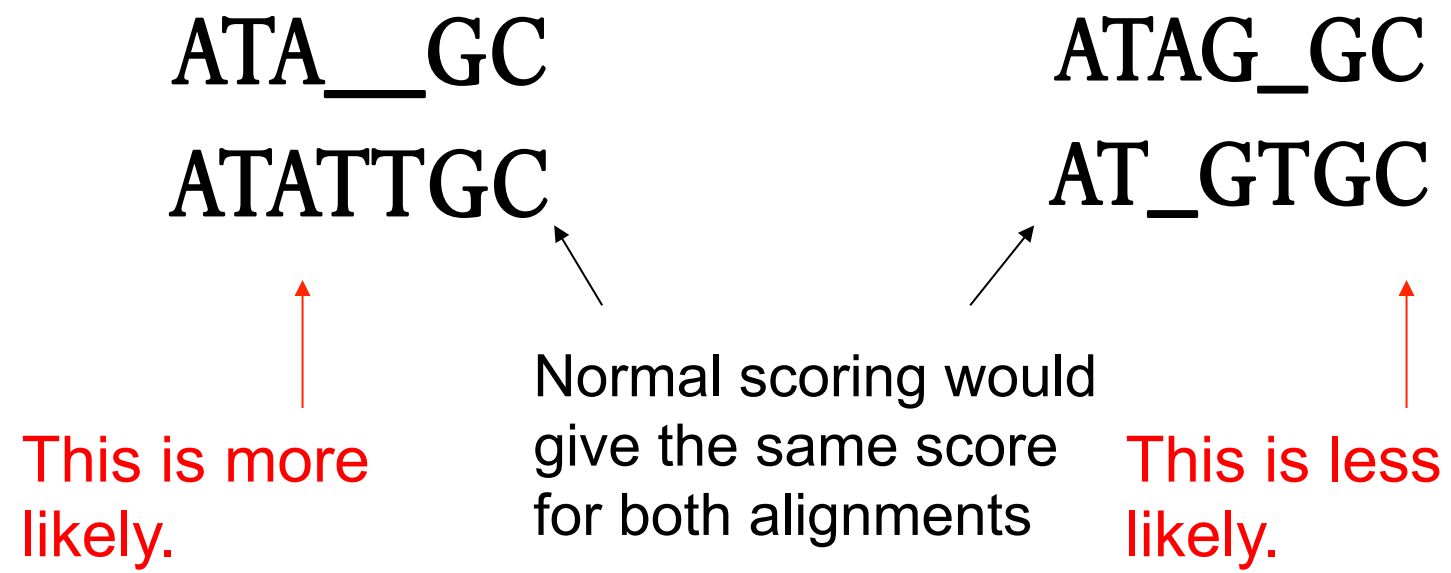
Affine Gap Penalties

- In nature, a series of *k* indels often come as a single event rather than a series of *k* single nucleotide events:



Accounting for Gaps

- *Gaps*- contiguous sequence of spaces in one of the rows

- Score for a gap of length x is: $-(\rho + \sigma x)$
  where $\rho > 0$ is the gap opening penalty
  ρ will be large relative to gap extension penalty σ

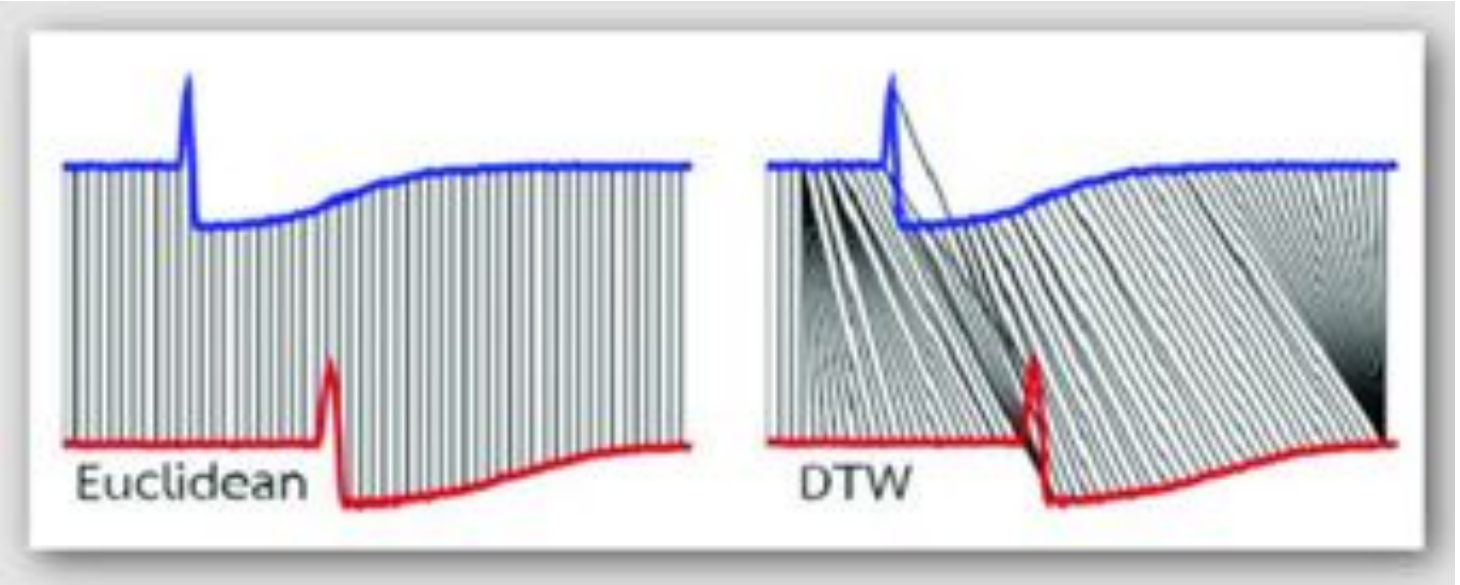
  - Gap of length 1: $-(\rho + \sigma) = -6$
  - Gap of length 2: $-(\rho + \sigma 2) = -7$
  - Gap of length 3: $-(\rho + \sigma 3) = -8$

- Smith-Waterman-Gotoh incorporates affine gap penalties without increasing the running time O(mn)

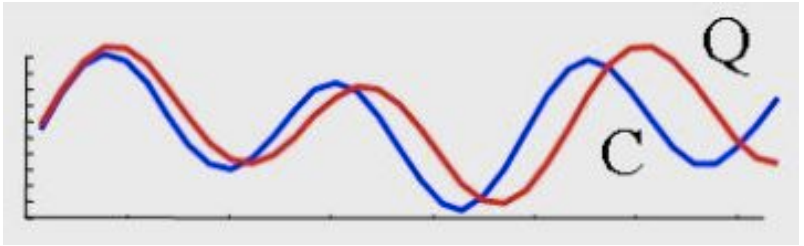
Break

Dynamic Time Warp

- Algorithm for measuring the similarity between two sequences of numeric values that vary in time or speed
  - Computes a non-linear mapping for sequence A to sequence B
  - Many applications for video, audio, and graphics
  - Speech processing: Recognize speech patterns coping with different speaking speeds
  - EEG processing: Identify anomalies in brain or heart activity



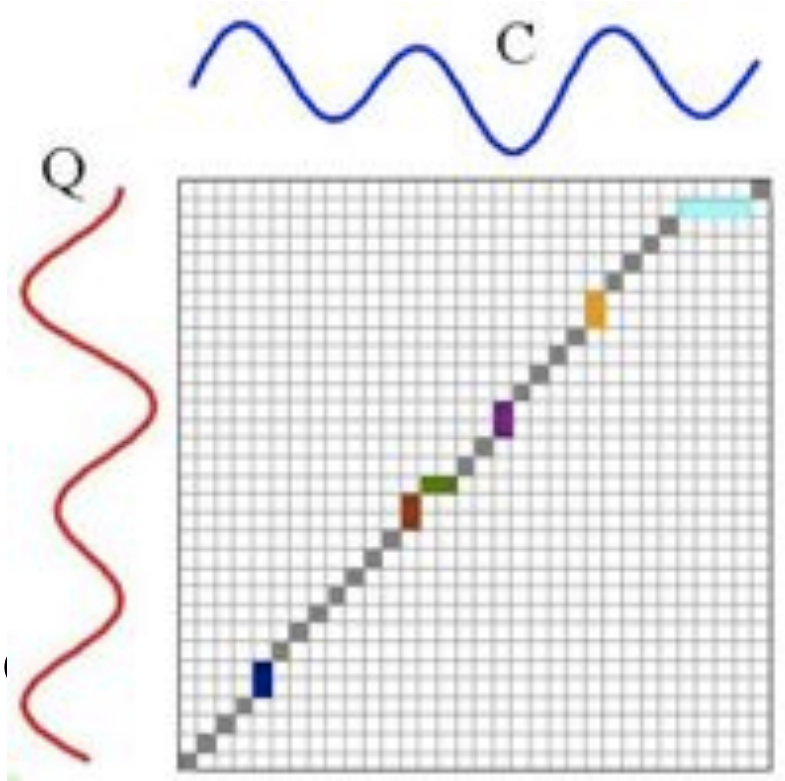
DTW Algorithm



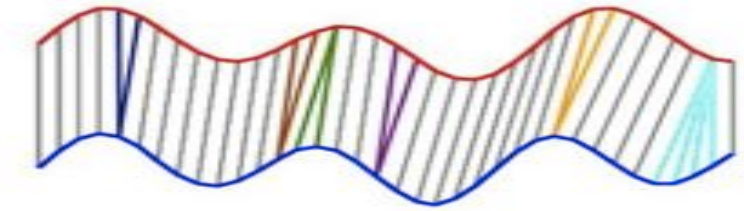
- *DP Algorithm*
  - Input: two time series C and Q
  - Compute the time warping matrix d

$$d(0,0) = 0;\ d(i,0) = d(0,j) = \infty$$

$$d(i,j) = |c_i - q_j| + \min \begin{cases} d(i-1, j) \\ d(i,j-1) \\ d(i-1, j-1) \end{cases}$$



- Warping matrix projects sequence C to sequence Q, allowing for non-linear contractions and expansions.



Basic Local Alignment Search Tool

- Rapidly compare a sequence Q to a database to find all sequences in the database with an score above some cutoff S.
  - Which protein is most similar to a newly sequenced one?
  - Where does this sequence of DNA originate?

- Speed achieved by using a procedure that typically finds "most" matches with scores > S.
  - Tradeoff between sensitivity and specificity/speed
    - Sensitivity – ability to find all related sequences
    - Specificity – ability to reject unrelated sequences

(Altschul et al. 1990)

Seed and Extend

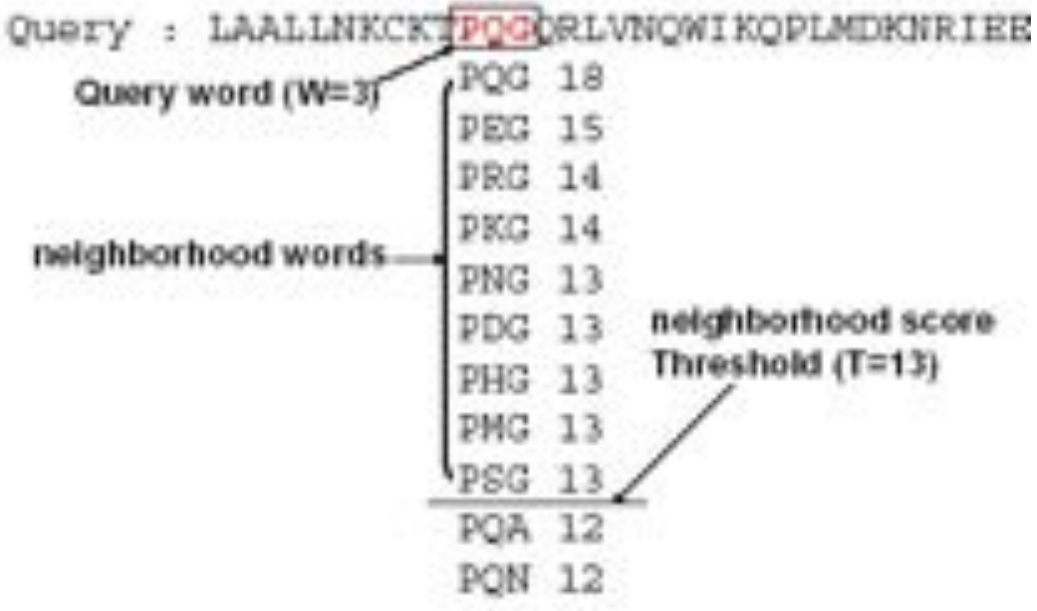
```
FAKDFLAGGVAAAISKTAVAPIERVKLLLQVQHASKQITADKQYKGIIDCVVRIPKEQGV
F  D  +GG AAA+SKTAVAPIERVKLLLQVQ ASK I  DK+YKGI+D ++R+PKEQGV
FLIDLASGGTAAAVSKTAVAPIERVKLLLQVQDASKAIAVDKRYKGIMDVLIRVPKEQGV
```

- Homologous sequence are likely to contain a short high scoring word pair, a seed.
  - Unlike *Baeza-Yates*, BLAST *doesn't* make explicit guarantees

- BLAST then tries to extend high scoring word pairs to compute maximal high scoring segment pairs (HSPs).
  - Heuristic algorithm but evaluates the result statistically.

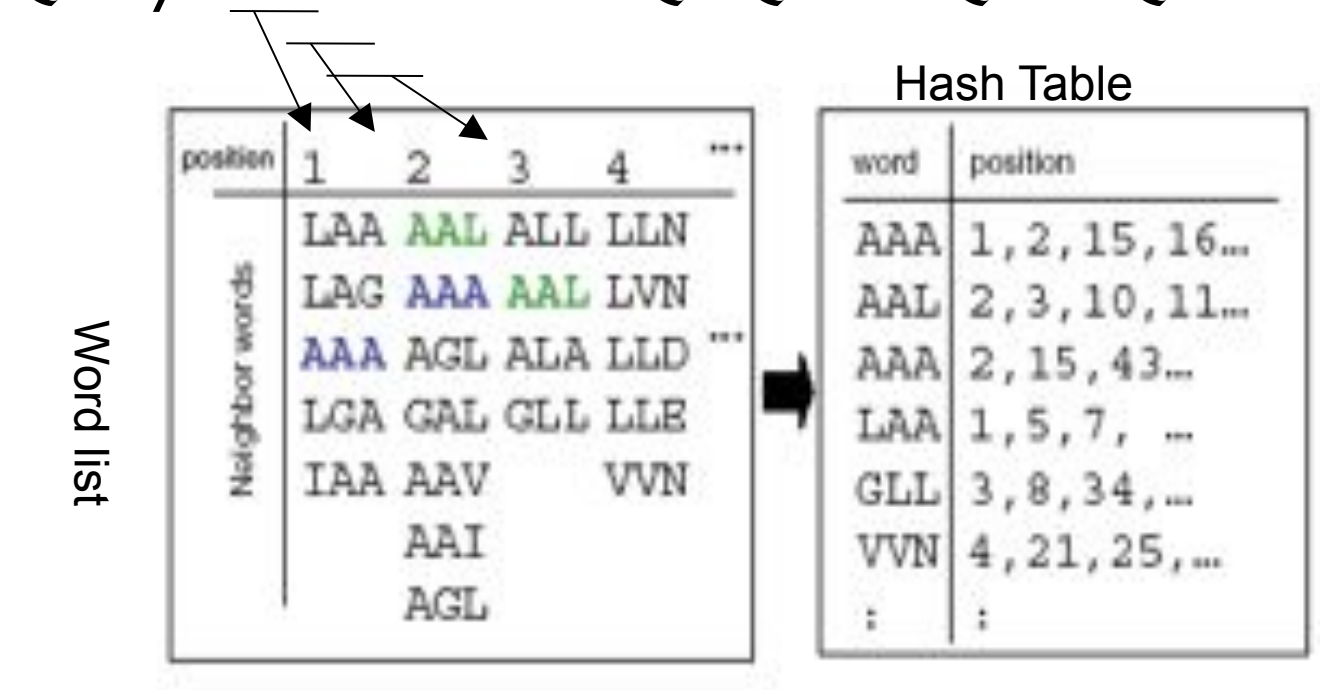
BLAST - Algorithm -

- Step 1: Preprocess Query
  Compile the short-high scoring word list from query.
  The length of query word, w, is 3 for protein scoring
  Threshold T is 13



BLAST - Algorithm -

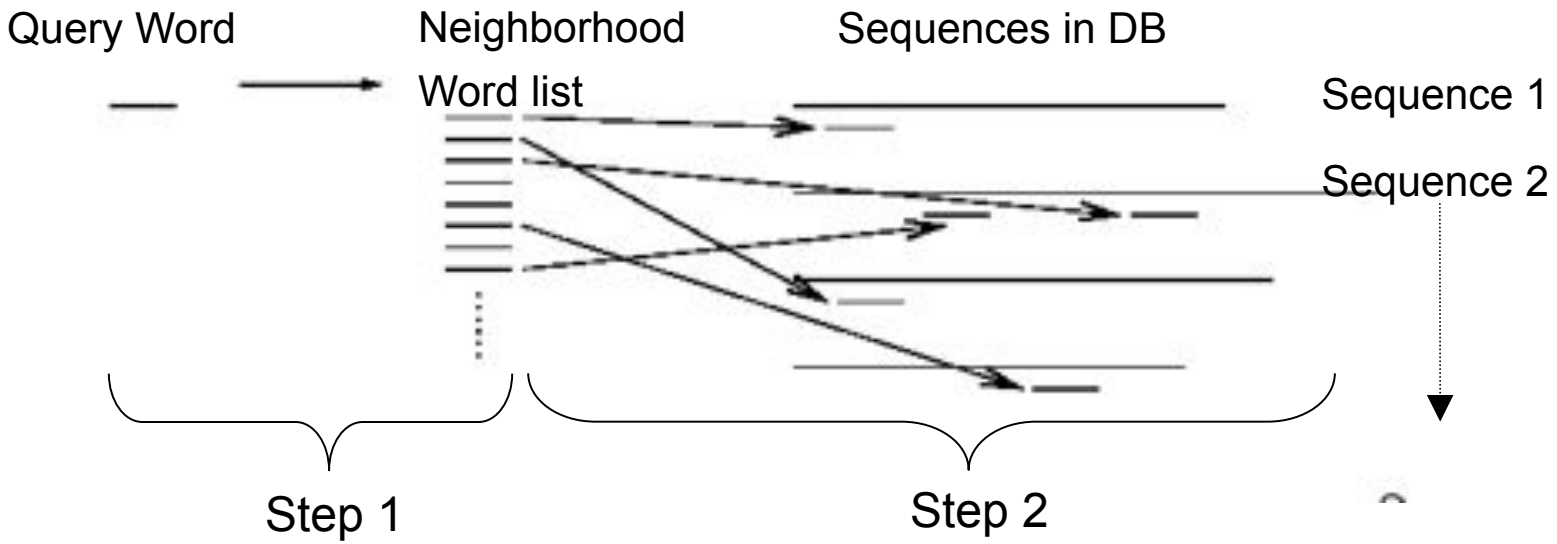
- Step 2: Construct Query Word Hash Table



BLAST - Algorithm -

- Step 3: Scanning DB

  Identify all exact matches with DB sequences



BLAST - Algorithm -

- Step 4 (Search optimal alignment)
  For each hit-word, extend ungapped alignments in both directions.
  Let S be a score of hit-word

- Step 5 (Evaluate the alignment statistically)
  Stop extension when E-value (depending on score S) become less than threshold. The extended match is called High Scoring Segment Pair.

E-value = the number of HSPs having score S (or higher) expected to occur by chance.

→ Smaller E-value, more significant in statistics

Bigger E-value , by chance

E[# occurrences of a string of length m in reference of length L] ~ $L/4^m$

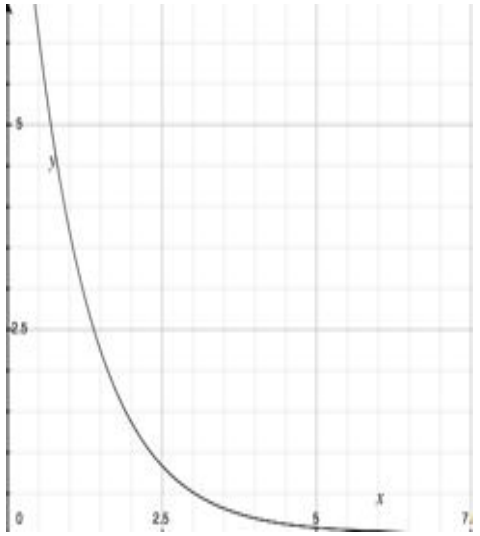
BLAST E-values

The expected number of HSPs with the score at least S is :

$$E = K*n*m*e^{-\lambda S}$$

K, λ are constant depending on model

n, m are the length of query and sequence



The probability of finding at least one such HSP is:

$$P = 1 - e^{E}$$

→ If a word is hit by chance (E-value is bigger), P become smaller.

The distribution of Smith-Waterman local alignment scores between two random sequences follows the Gumbel extreme value distribution

Very Similar Sequences

```
Query: HBA_HUMAN Hemoglobin alpha subunit
Sbjct: HBB_HUMAN Hemoglobin beta subunit

Score =  114 bits (285),  Expect = 1e-26
Identities = 61/145 (42%), Positives = 86/145 (59%), Gaps = 8/145 (5%)

Query  2   LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF------DLSHGSAQV 55
           L+P +K+ V A WGKV  +  E G EAL R+ + +P T+ +F  F       D   G+ +V
Sbjct  3   LTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKV 60

Query  56  KGHGKKVADALTNAVAHVDDMPNALSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAHLPA 115
           K HGKKV  A ++ +AH+D++    + LS+LH  KL VDP NF+LL + L+  LA H
Sbjct  61  KAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGK 120

Query  116 EFTPAVHASLDKFLASVSTVLTSKY 140
           EFTP V A+  K +A V+  L  KY
Sbjct  121 EFTPPVQAAYQKVVAGVANALAHKY 145
```

Quite Similar Sequences

```
Query: HBA_HUMAN Hemoglobin alpha subunit
Sbjct: MYG_HUMAN Myoglobin

Score = 51.2 bits (121), Expect = 1e-07,
Identities = 38/146 (26%), Positives = 58/146 (39%), Gaps = 6/146 (4%)

Query  2   LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF------DLSHGSAQV  55
           LS  +   V   WGKV A    +G E L R+F   P T   F  F      D    S  +
Sbjct  3   LSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETLEKFDKFKHLKSEDEMKASEDL  62

Query  56  KGHGKKVADALTNAVAHVDDMPNALSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAHLPA  115
           K HG  V  AL   +          +  L+  HA K ++     + +S C++  L +  P
Sbjct  63  KKHGATVLTALGGILKKKGHHEAEIKPLAQSHATKHKIPVKYLEFISECIIQVLQSKHPG  122

Query  116 EFTPAVHASLDKFLASVSTVLTSKYR  141
            +F      +++K L      + S Y+
Sbjct  123 DFGADAQGAMNKALELFRKDMASNYK  148
```

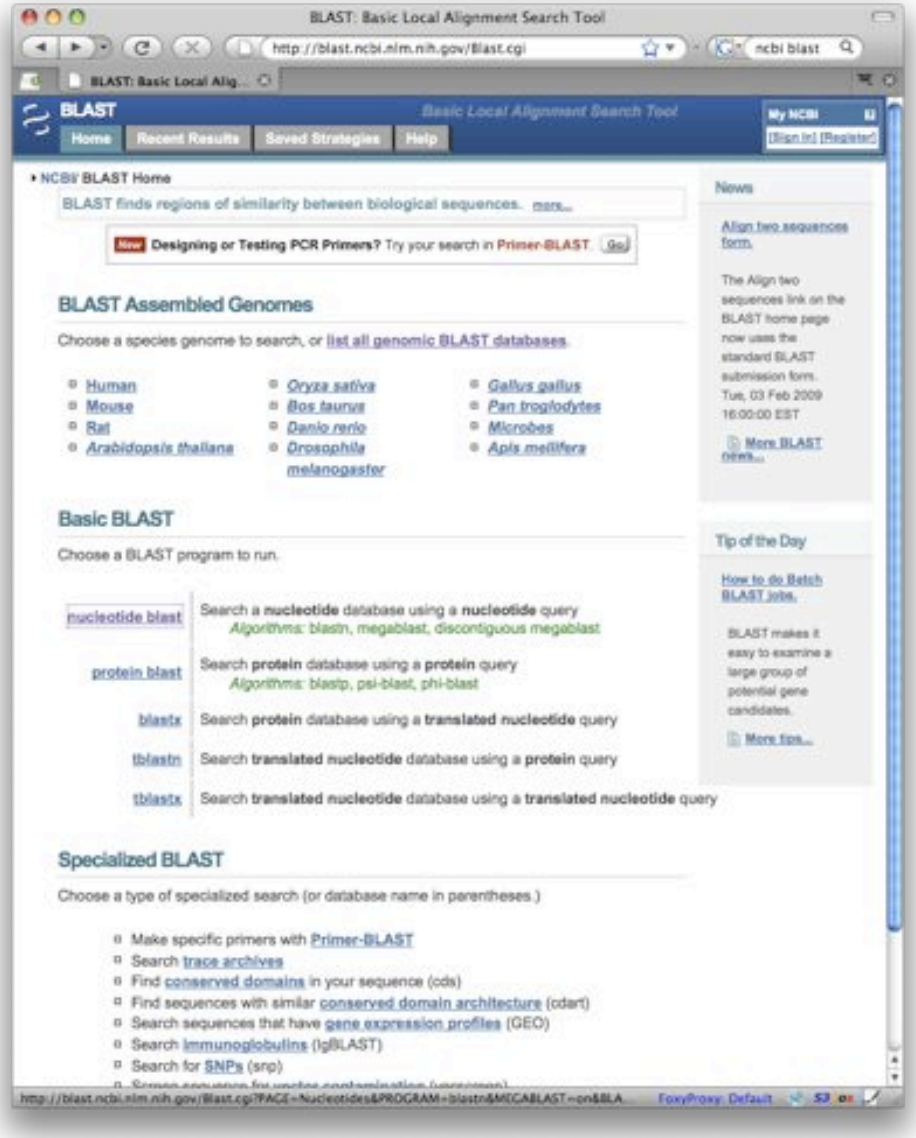
Not similar sequences

```
Query: HBA_HUMAN Hemoglobin alpha subunit
Sbjct: SPAC869.02c [Schizosaccharomyces pombe]

 Score = 33.1 bits (74),  Expect = 0.24
 Identities = 27/95 (28%), Positives = 50/95 (52%), Gaps = 10/95 (10%)

Query  30  ERMFLSFPTTKTYFPHFDLSHGSAQVKGHGKKVADALTNAVAHVDDMPNALSALSDLHAH  89
           ++M  ++P      P+F+ +H  +      + +A AL N   ++DD+  +LSA  D
Sbjct  59  QKMLGNYPEV---LPYFNKAHQISL--SQPRILAFALLNYAKNIDDL-TSLSAFMDQIVV 112

Query  90  K---LRVDPVNFKLLSHCLLVTLAAHLPAEF-TPA  120
           K   L++   ++ ++ HCLL T+   LP++  TPA
Sbjct  113 KHVGLQIKAEHYPIVGHCLLSTMQELLPSDVATPA  147
```

Blast Versions

Program	Database	Query
BLASTN	Nucleotide	Nucleotide
BLASTP	Protein	Protein
BLASTX	Protein	Nucleotide translated in to protein
TBLASTN	Nucleotide translated in to protein	Protein
TBLASTX	Nucleotide translated in to protein	Nucleotide translated in to protein

NCBI Blast



- Nucleotide Databases
  - nr: All Genbank
  - refseq: Reference organisms
  - wgs: All reads

- Protein Databases
  - nr: All non-redundant sequences
  - Refseq: Reference proteins

BLAST Exercise

>whoami

TTGATGCAGGTATCTGCGACTGAGACAATATGCA
ACAGTTGAATGAATCATAATGGAATGTGCACTCT
AACCAGCCAATTTGATGCTGGCTGCAGAGATGC
AAGATCAAGAGGTGACACCTGCTCTGAAGAAAG
CACAGTTGAACTGCTGGATCTGCAACTACAGCA
GGCACTCCAGGCACCAAGACAACATCTTTTACA
CCAGCAAACATGTGGATTGATATCTCCTAACAGC
AGTGATTAACAGAGACGACTGCAGGATTTGCTTC
CACAAACAAAAT

Parameters

- Larger values of w increases the number of neighborhood words, but decreases the number of chance matches in the database.
  - Increasing w decreases sensitivity.

- Larger values of T decrease the overall execution time, but increase the chance of missing a MSP having score ≥ S.
  - Increases T decreases the sensitivity

- Larger values of S increase the specificity. The value of S is affected by changes in the expectation value parameter.

Sequence Alignment Summary

- Distance metrics:
  - Hamming: How many substitutions?
  - Edit Distance: How many substitutions or indels?
  - Sequence Similarity: How similar (under this model of similarity)?

- Techniques
  - Seed-and-extend: Anchor the search for in-exact using exact only
  - Dynamic Programming: Find a global optimal as a function of its parts
  - BWT Search: implicit DFS of SA/ST

- Sequence Alignment Algorithms: Pick the right tool for the job
  - Smith-Waterman: DP Local sequence alignment
  - BLAST: Homology Searching
  - Bowtie/BWA/Novoalign: short read mapping