CS481/CS583: Bioinformatics Algorithms

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SIMILARITY SEARCH

Heuristic Similarity Searches

- Genomes are huge: Smith-Waterman quadratic alignment algorithms are too slow
- Alignment of two sequences usually has short identical or highly similar fragments
- Many heuristic methods (i.e., FASTA) are based on the same idea of *filtration*
  - Find short exact matches, and use them as seeds for potential match extension
  - “Filter” out positions with no extendable matches

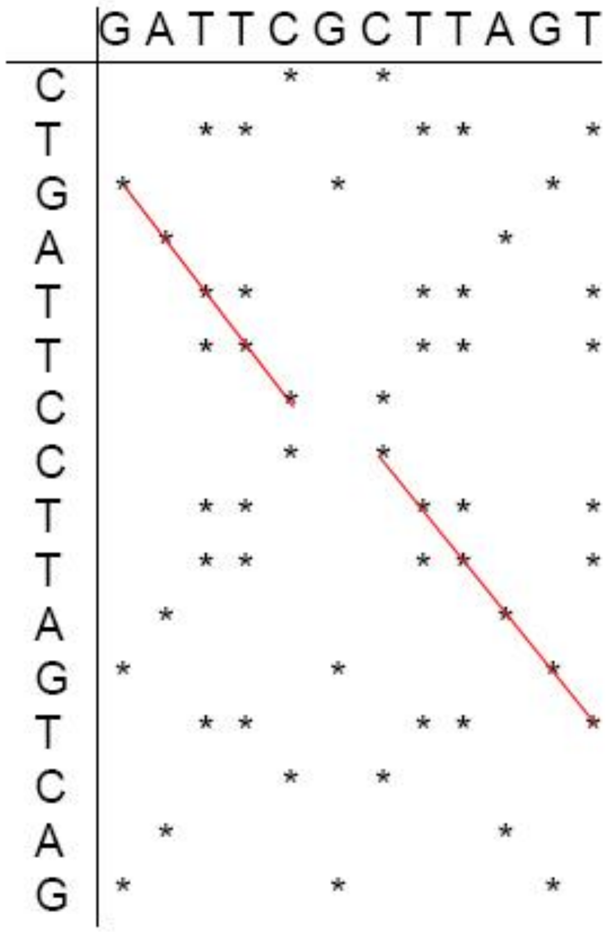
Dot Matrices

- Dot matrices show similarities between two sequences
- FASTA makes an implicit dot matrix from short exact matches, and tries to find long diagonals (allowing for some mismatches)

	G	A	T	T	C	G	C	T	T	A	G	T
C					*		*					
T			*	*				*	*			*
G	*					*					*	
A		*								*		
T			*	*				*	*			*
T			*	*				*	*			*
C					*		*					
C					*		*					
T			*	*				*	*			*
T			*	*				*	*			*
A		*								*		
G	*					*					*	
T			*	*				*	*			*
C					*		*					
A		*								*		
G	*					*					*	

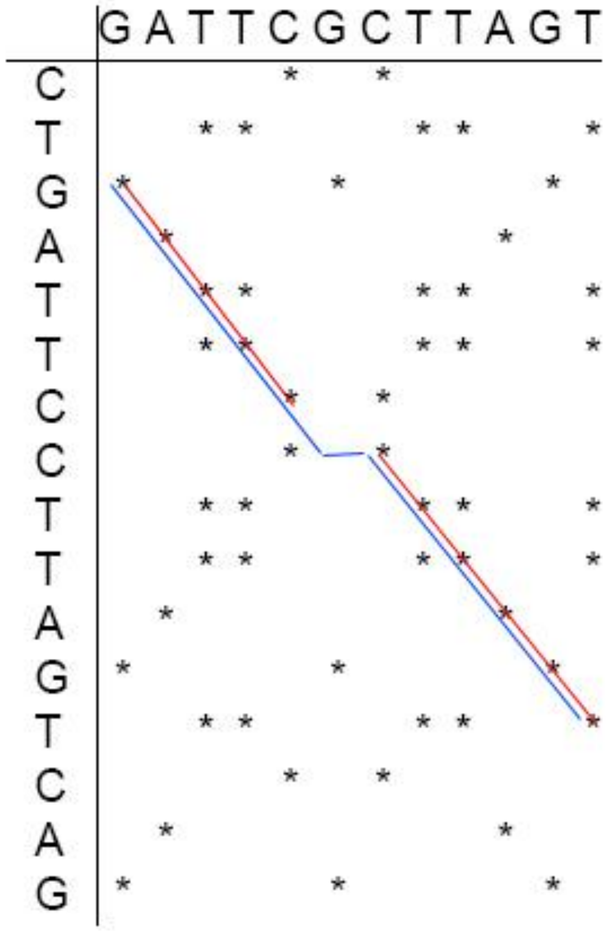
Dot Matrices (cont'd)

- Identify diagonals above a threshold length
- Diagonals in the dot matrix indicate exact substring matching



Diagonals in Dot Matrices

- Extend diagonals and try to link them together, allowing for minimal mismatches/indels
- Linking diagonals reveals approximate matches over longer substrings



Approximate Pattern Matching Problem

- Goal: *Find all approximate occurrences of a pattern in a text*
- Input: A pattern $\mathbf{p} = p_1 \ldots p_n$, text $\mathbf{t} = t_1 \ldots t_m$, and k, the maximum number of mismatches
- Output: All positions $1 \leq i \leq (m - n + 1)$ such that $t_i \ldots t_{i+n-1}$ and $p_1 \ldots p_n$ have at most k mismatches (i.e., Hamming distance between $t_i \ldots t_{i+n-1}$ and $\mathbf{p} \leq k$)

Approximate Pattern Matching: A Brute-Force Algorithm

```
ApproximatePatternMatching(p, t, k)
n □ length of pattern p
m □ length of text t
for i □ 1 to m – n + 1
   dist □ 0
   for j □ 1 to n
      if $t_{i+j-1}$ != $p_j$
         dist □ dist + 1
   if dist ≤ k
      output i
```

Approximate Pattern Matching: Running Time

- That algorithm runs in O(*nm*).
- We can generalize the "Approximate Pattern Matching Problem" into a "Query Matching Problem":
  - We want to match substrings in a query to substrings in a text with at most ***k*** mismatches
  - **Motivation**: we want to see similarities to some gene, but we may not know which parts of the gene to look for

Query Matching Problem

- Goal: *Find all substrings of the query that approximately match the text*
- Input: Query **q** = $q_1 \ldots q_w$,
  text **t** = $t_1 \ldots t_m$,
  n (length of matching substrings),
  k (maximum number of mismatches)
- Output: All pairs of positions (*i*, *j*) such that the
  n-letter substring of **q** starting at *i*
  approximately matches the
  n-letter substring of **t** starting at *j*,
  with at most *k* mismatches

Query Matching: Main Idea

- Approximately matching strings share some perfectly matching substrings.
- Instead of searching for approximately matching strings (difficult) search for perfectly matching substrings (easy).

Filtration in Query Matching

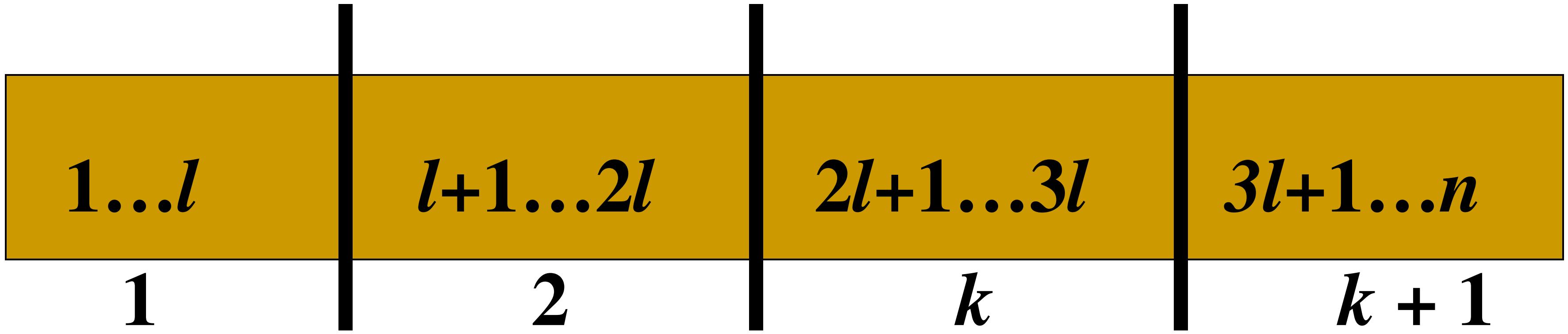
- We want all *n*-matches between a query and a text with up to *k* mismatches
- "Filter" out positions we know do not match between text and query
- **Potential match detection**: find all matches of ℓ-tuples in query and text for some small ℓ
- **Potential match verification**: Verify each potential match by extending it to the left and right, until (k + 1) mismatches are found

Filtration: Match Detection

- If $x_1 \ldots x_n$ and $y_1 \ldots y_n$ match with at most k mismatches, they must share an ℓ-tuple that is perfectly matched, with $\ell = \lfloor n/(k+1) \rfloor$
- Break string of length n into k+1 parts, each each of length $\lfloor n/(k+1) \rfloor$
  - k mismatches can affect at most k of these k+1 parts
  - At least one of these k+1 parts is perfectly matched

Filtration: Match Detection (cont'd)

- Suppose $k = 3$. We would then have $l=n/(k+1)=n/4$:

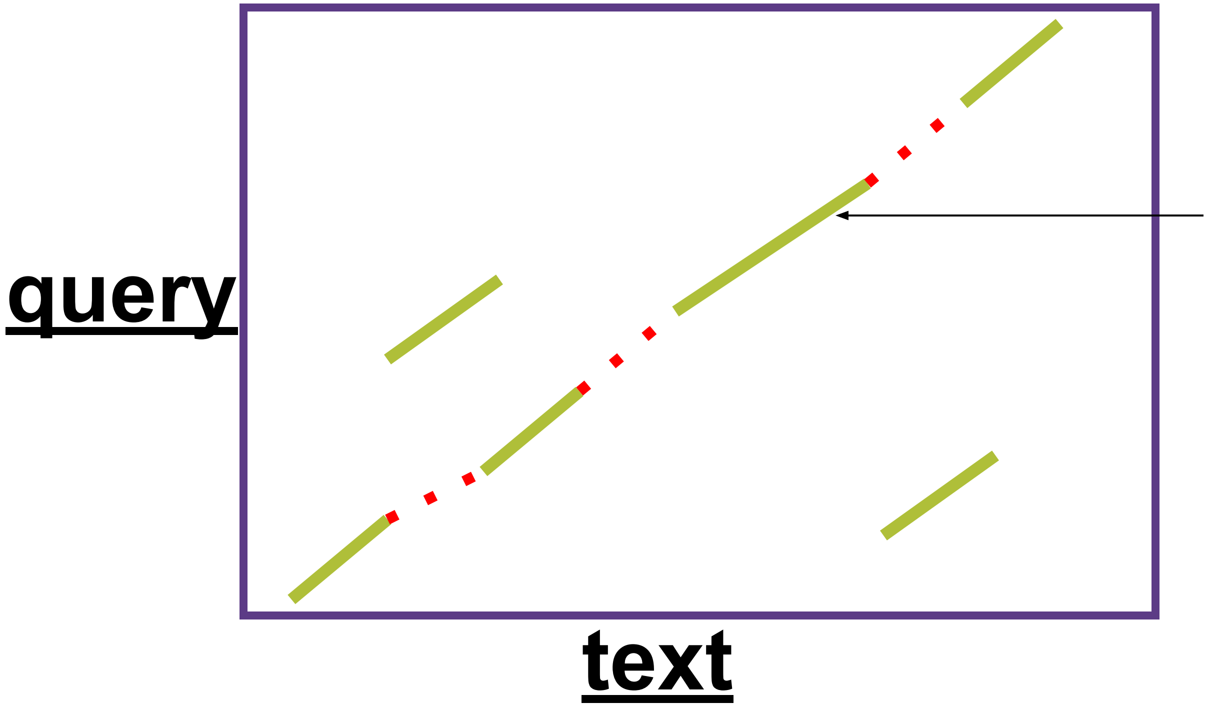


- There are at most k mismatches in n, so at the very least there must be one out of the $k+1$ ℓ–tuples without a mismatch

What is this based on?

Filtration: Match Verification

- For each ℓ-match we find, try to extend the match further to see if it is substantial



Extend perfect match of length ℓ
until we find an approximate match of length *n* with *k* mismatches

Filtration: Example

	k = 0	***k*** = 1	***k*** = 2	***k*** = 3	***k*** = 4	***k*** = 5
ℓ-tuple length	***n***	***n***/2	***n***/3	***n***/4	***n***/5	***n***/6

Shorter perfect matches required

Performance decreases

Lipman & Pearson, 1985

FASTP

FASTP

- Three phase algorithm

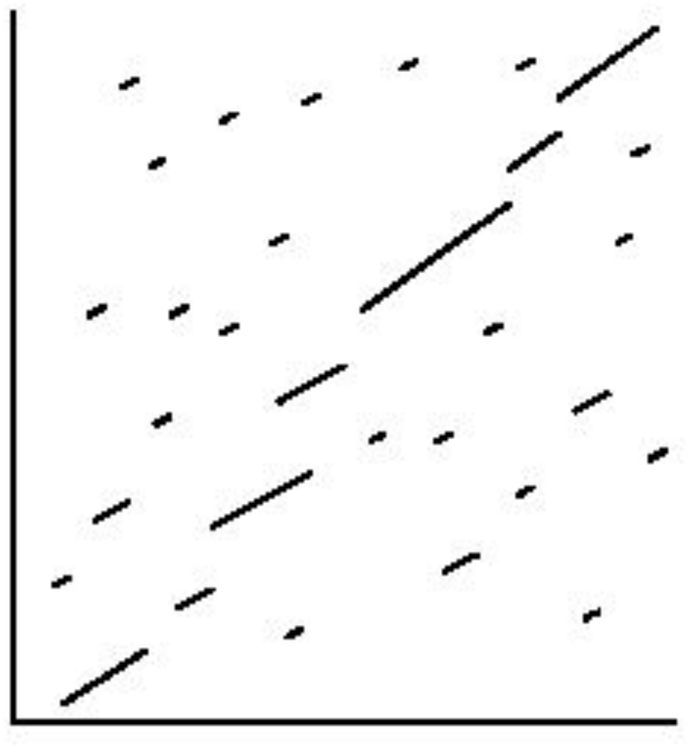
1. Find short good matches using k-mers
    1. k=1, k=2
2. Find start and end positions for good matches
3. Use DP to align good matches

FASTP: Phase 1 (1)

```
position   1 2 3 4 5 6 7 8 9 10 11
protein 1 n c s p t a . . . . .
protein 2 . . . . . a c s p r k
                    position in          offset
amino acid        protein 1 protein 2   pos 1 – pos2
-----------------------------------------------------
a                   6         6              0
c                   2         7             -5
k                   -        11
n                   1         -
p                   4         9             -5
r                   -        10
s                   3         8             -5
t                   5         -
-----------------------------------------------------
Note the common offset for the 3 amino acids c,s and p
A possible alignment can be quickly found :
protein 1 n c s p t a
            | | |
protein 2 a c s p r k
```

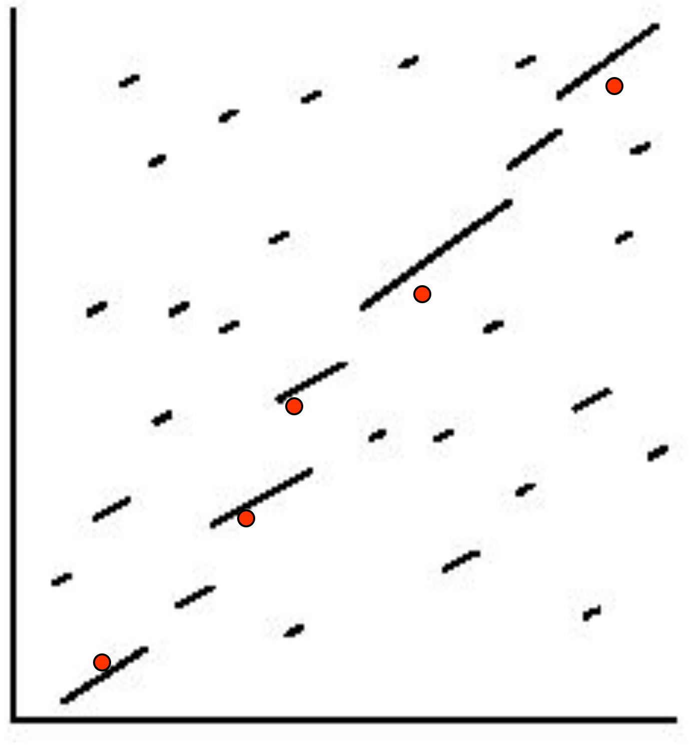
FASTP: Phase 1 (2)

- Similar to dot plot
- Offsets range from 1-m to n-1
- Each offset is scored as
  - # matches - # mismatches
- Diagonals (offsets) with large score show local similarities



FASTP: Phase 2

- 5 best diagonal runs are found
- Rescore these 5 regions using PAM250.
    - Initial score
- Indels are not considered yet



FASTP: Phase 3

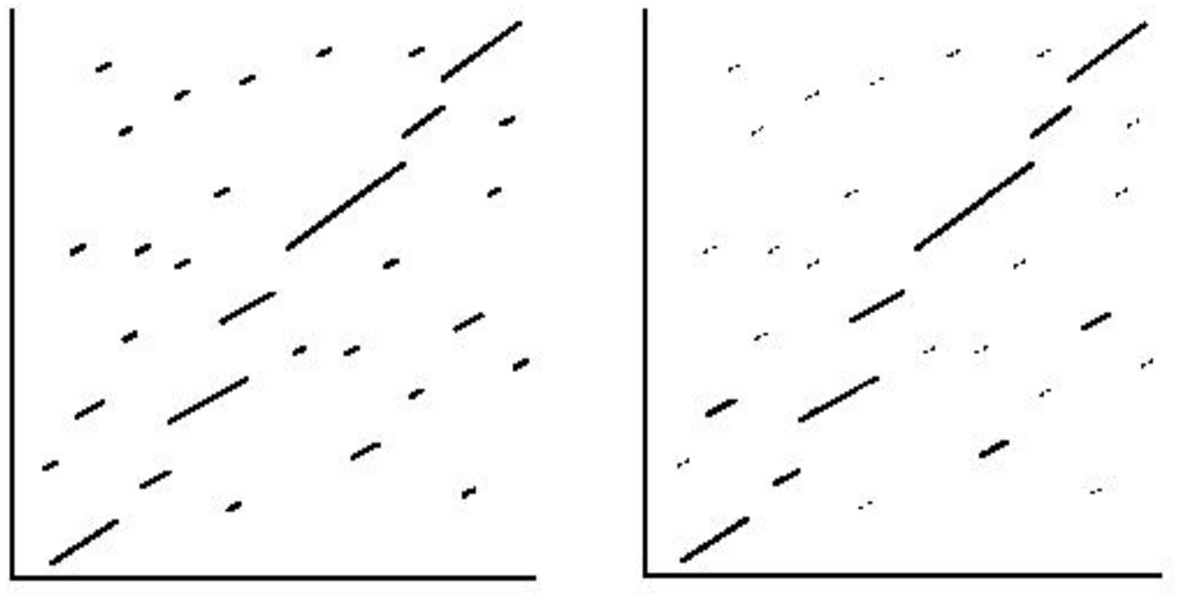
- Sort the aligned regions in descending score
- Optimize these alignments using Needleman-Wunsch
- Report the results

Pearson 1995

FASTA – IMPROVEMENT OVER FASTP

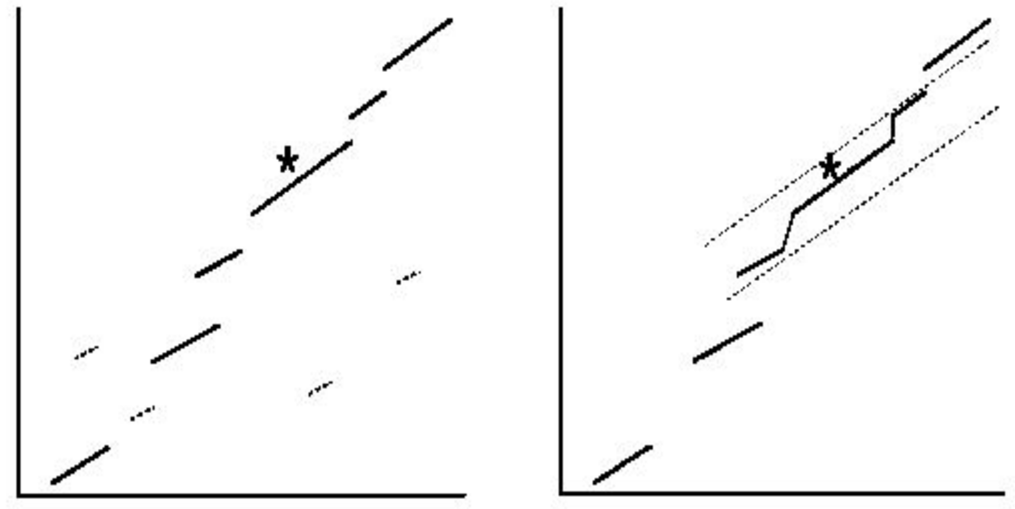
FASTA (1)

- Phase 2: Choose 10 best diagonal runs instead of 5



FASTA (2)

- Phase 2.5
  - Eliminate diagonals that score less than some given threshold.
  - Combine matches to find longer matches. It incurs join penalty similar to gap penalty



FASTA Variations

- TFASTAX and TFASTAY: query protein against a DNA library in all reading frames
- FASTAX, FASTAY: DNA query in all reading frames against protein database

BLAST

Local alignment is too slow…

- Quadratic local alignment is too slow while looking for similarities between long strings (e.g. the entire GenBank database)

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

Local alignment is too slow…

- Quadratic local alignment is too slow while looking for similarities between long strings (e.g. the entire GenBank database)
- Guaranteed to find the optimal local alignment
- Sets the standard for sensitivity

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

Local alignment is too slow…

- Quadratic local alignment is too slow while looking for similarities between long strings (e.g. the entire GenBank database)
- **B**asic **L**ocal **A**lignment **S**earch **T**ool
  - Altschul, S., Gish, W., Miller, W., Myers, E. & Lipman, D.J.

    Journal of Mol. Biol., 1990
- Search sequence databases for local alignments to a query

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

BLAST

- Great improvement in speed, with a modest decrease in sensitivity
- Minimizes search space instead of exploring entire search space between two sequences
- Finds short exact matches (“seeds”), only explores locally around these “hits”
  - “Seed-and-extend”

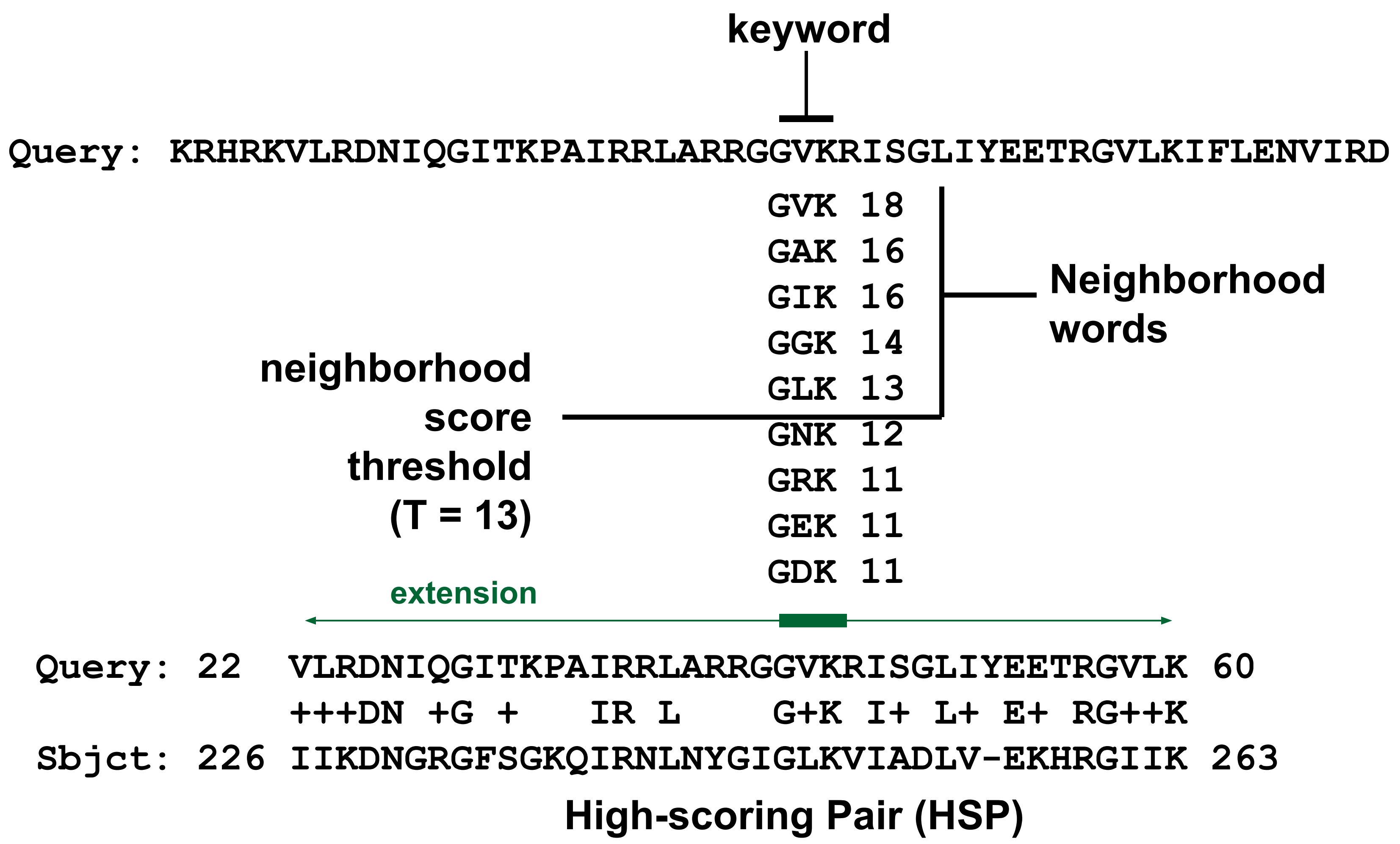
What Similarity Reveals

- BLASTing a new gene
    - Evolutionary relationship
    - Similarity between protein function
- BLASTing a genome
    - Potential genes

BLAST algorithm

- Keyword search of all words of length *w* from the query of length *n* in database of length *m* with score above threshold
  - *w* = 11 for DNA queries, *w* =3 for proteins
  - For each k-mer *w* find all k-mer that aligns with score at least cutoff T
- Local alignment extension for each found keyword
  - Extend result until longest match above threshold is achieved
- Running time O(*nm*)

BLAST algorithm (cont'd)



```
Query: KRHRKVLRDNIQGITKPAIRRLARRGGVKRISGLIYEETRGVLKIFLENVIRD
                                 GVK 18
                                 GAK 16
                                 GIK 16
                                 GGK 14
                                 GLK 13
                                 GNK 12
                                 GRK 11
                                 GEK 11
                                 GDK 11
```

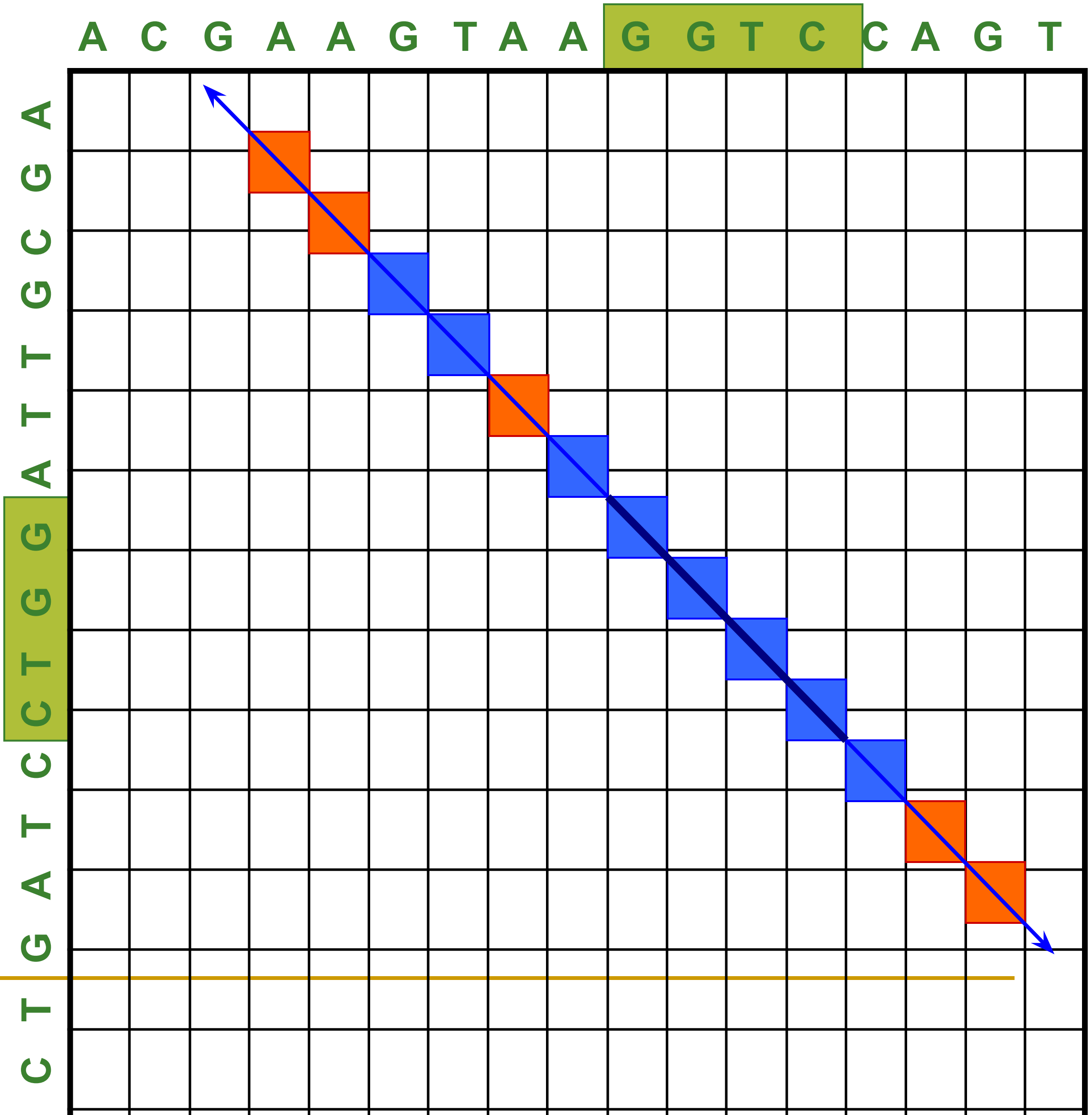
```
Query:  22  VLRDNIQGITKPAIRRLARRGGVKRISGLIYEETRGVLK 60
            +++DN +G +    IR L      G+K I+ L+ E+ RG++K
Sbjct: 226 IIKDNGRGFSGKQIRNLNYGIGLKVIADLV-EKHRGIIK 263
```

Original BLAST

- **Dictionary**
  - All words of length *w*
- **Alignment**
  - *Ungapped* extensions until score falls below some statistical threshold
- **Output**
  - All local alignments with score > threshold

Original BLAST: Example

- *w* = 4
- Exact keyword match of GGTC
- Extend diagonals with mismatches until score is under 50%
- Output result
  GTAAGGTCC
  GTTAGGTCC



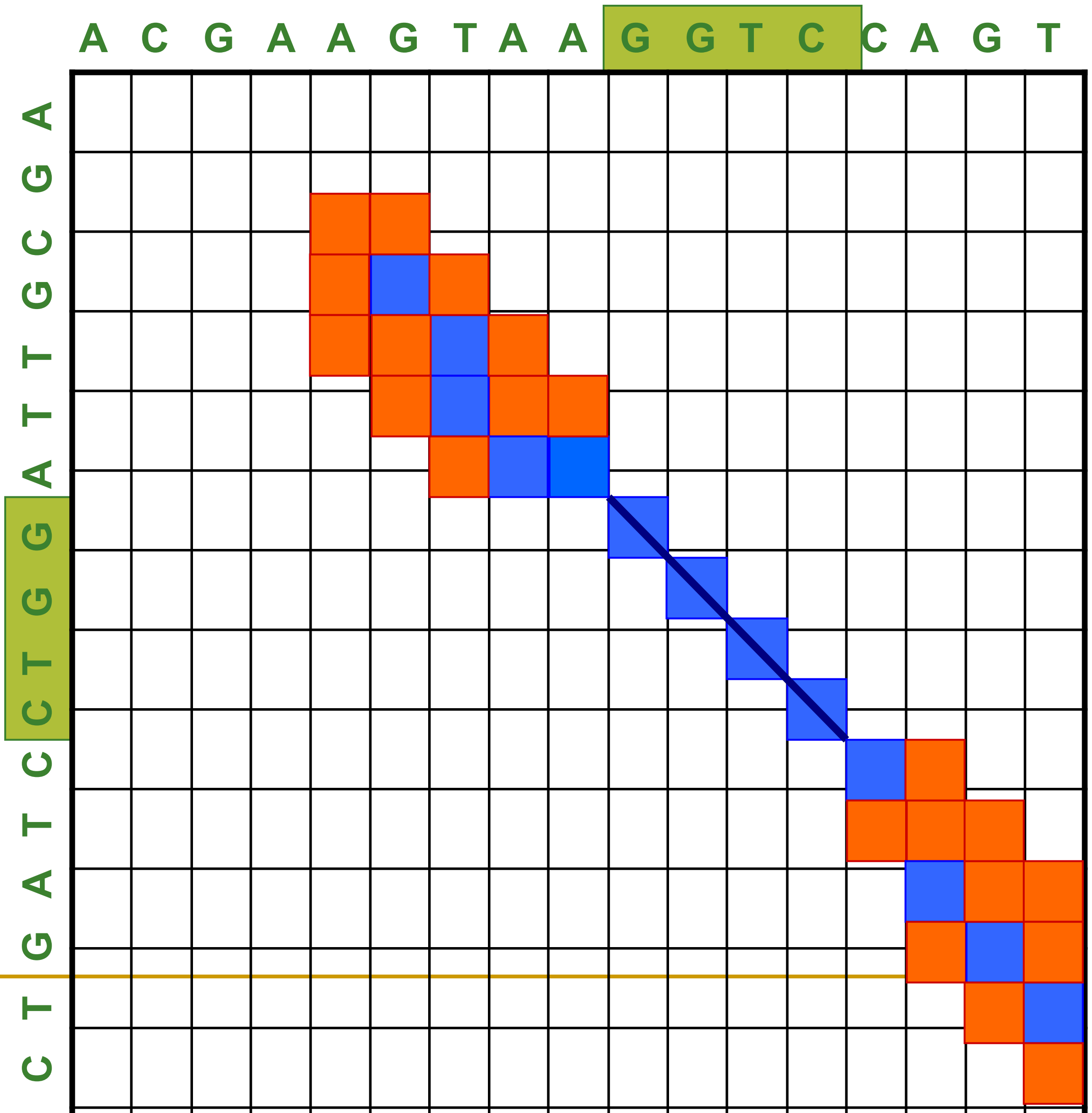
A C G A A G T A A G G T C C A G T
A G C G T T A G G T C C T A G T C

From lectures by Serafim Batzoglou (Stanford)

Gapped BLAST : Example

- Original BLAST exact keyword search, THEN:
- Extend with gaps around ends of exact match until score < *threshold*
- Output result

GTAAGGTCCAGT
GTTAGGTC-AGT


A C G A A G T A A G G T C C A G T
A G C G T T A G G T C C T A G T C

From lectures by Serafim Batzoglou (Stanford)

Incarnations of BLAST

- blastn: Nucleotide-nucleotide
- blastp: Protein-protein
- blastx: Translated query vs. protein database
- tblastn: Protein query vs. translated database
- tblastx: Translated query vs. translated database (6 frames each)

Incarnations of BLAST (cont'd)

- PSI-BLAST
  - Find members of a protein family or build a custom position-specific score matrix
- Megablast:
  - Search longer sequences with fewer differences
- WU-BLAST: (Wash U BLAST)
  - Optimized, added features

ASSESSING SEQUENCE SIMILARITY

Assessing sequence similarity

- Need to know how strong an alignment can be expected from chance alone
- “Chance” relates to comparison of sequences that are generated randomly based upon a certain sequence model
- Sequence models may take into account:
  - G+C content
  - Poly-A tails
  - “Junk” DNA
  - Codon bias
  - Etc.

BLAST: Segment Score

- BLAST uses scoring matrices (δ) to improve on efficiency of match detection
  - Some proteins may have very different amino acid sequences, but are still similar
- For any two ℓ-mers $x_1 \ldots x_\ell$ and $y_1 \ldots y_\ell$:
  - <u>Segment pair</u>: pair of ℓ-mers, one from each sequence
  - <u>Segment score</u>: $\Sigma^{\ell}_{i=1}\ \delta(x_i, y_i)$

BLAST: Locally Maximal Segment Pairs

- A segment pair is <u>maximal</u> if it has the best score over all segment pairs
- A segment pair is <u>locally maximal</u> if its score can't be improved by extending or shortening
- Statistically significant *locally maximal* segment pairs are of biological interest
- BLAST finds all locally maximal segment pairs with scores above some threshold
  - A significantly high threshold will filter out some statistically insignificant matches

BLAST: Statistics

- Threshold: Altschul-Dembo-Karlin statistics
  - Identifies smallest segment score that is unlikely to happen by chance
- # matches above θ has mean $E(\theta) = Kmne^{-\lambda\theta}$; K is a constant, m and n are the lengths of the two compared sequences
  - Parameter λ is positive root of:

    $\Sigma_{x,y \text{ in } A}(p_x p_y e^{\delta(x,y)}) = 1$, where p_x and p_y are frequencies of amino acids x and y, and A is the twenty letter amino acid alphabet

P-values

- The probability of finding *b* high-scoring segment pairs (HSPs) with a score $\geq S$ is given by:
  - $(e^{-E}E^{b})/b!$
- For $b = 0$, that chance is:
  - e^{-E}
- Thus the probability of finding at least one HSP with a score $\geq S$ is:
  - $P = 1 - e^{-E}$

Sample BLAST output

- **Blast of human beta globin protein against zebra fish**

```
                                                                 Score    E
Sequences producing significant alignments:                      (bits) Value

gi|18858329|ref|NP_571095.1| ba1 globin [Danio rerio] >gi|147757...   171   3e-44
gi|18858331|ref|NP_571096.1| ba2 globin; SI:dZ118J2.3 [Danio rer...   170   7e-44
gi|37606100|emb|CAE48992.1| SI:bY187G17.6 (novel beta globin) [D...   170   7e-44
gi|31419195|gb|AAH53176.1| Ba1 protein [Danio rerio]                  168   3e-43

ALIGNMENTS
>gi|18858329|ref|NP_571095.1| ba1 globin [Danio rerio]
Length = 148

 Score =  171 bits (434), Expect = 3e-44
 Identities = 76/148 (51%), Positives = 106/148 (71%), Gaps = 1/148 (0%)

Query: 1   MVHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPK 60
            MV  T  E++A+  LWGK+N+DE+G +AL R L+VYPWTQR+F +FG+LS+P A+MGNPK
Sbjct: 1   MVEWTDAERTAILGLWGKLNIDEIGPQALSRCLIVYPWTQRYFATFGNLSSPAAIMGNPK 60

Query: 61  VKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFG 120
            V AHG+ V+G      + ++DN+K T+A LS +H +KLHVDP+NFRLL + +    A  FG
Sbjct: 61  VAAHGRTVMGGLERAIKNMDNVKNTYAALSVMHSEKLHVDPDNFRLLADCITVCAAMKFG 120

Query: 121 KE-FTPPVQAAYQKVVAGVANALAHKYH 147
             +  F   VQ A+QK +A V +AL  +YH
Sbjct: 121 QAGFNADVQEAWQKFLAVVVSALCRQYH 148
```

Sample BLAST output (cont'd)

- **Blast of human beta globin DNA against human DNA**

```
                                                                       Score    E
Sequences producing significant alignments:                           (bits) Value

gi|19849266|gb|AF487523.1| Homo sapiens gamma A hemoglobin (HBG1...   289   1e-75
gi|183868|gb|M11427.1|HUMHBG3E Human gamma-globin mRNA, 3' end        289   1e-75
gi|44887617|gb|AY534688.1| Homo sapiens A-gamma globin (HBG1) ge...   280   1e-72
gi|31726|emb|V00512.1|HSGGL1 Human messenger RNA for gamma-globin     260   1e-66
gi|38683401|ref|NR_001589.1| Homo sapiens hemoglobin, beta pseud...   151   7e-34
gi|18462073|gb|AF339400.1| Homo sapiens haplotype PB26 beta-glob...   149   3e-33

ALIGNMENTS
>gi|28380636|ref|NG_000007.3| Homo sapiens beta globin region (HBB@) on chromosome 11
          Length = 81706
 Score =  149 bits (75), Expect = 3e-33
 Identities = 183/219 (83%)
 Strand = Plus / Plus

Query: 267   ttgggagatgccacaaagcacctggatgatctcaagggcacctttgcccagctgagtgaa 326
             || ||| | ||    | || |  |||||| ||||| |||||||||||    ||||||||
Sbjct: 54409 ttcggaaaagctgttatgctcacggatgacctcaaaggcacctttgctacactgagtgac 54468


Query: 327   ctgcactgtgacaagctgcatgtggatcctgagaacttc 365
             ||||||||| |||||||||| ||||| ||||||||||||
Sbjct: 54469 ctgcactgtaacaagctgcacgtggaccctgagaacttc 54507
```

Timeline

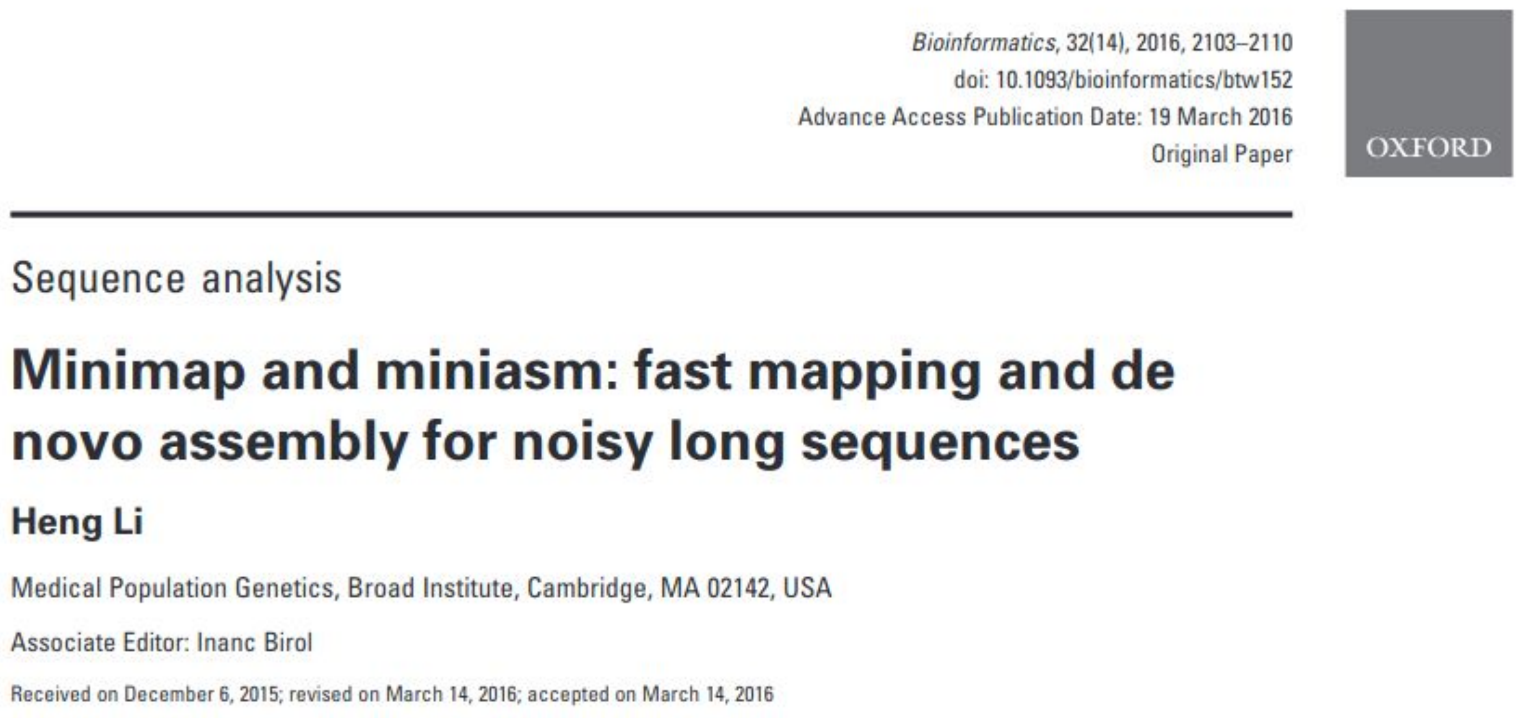
- 1970: Needleman-Wunsch global alignment algorithm
- 1981: Smith-Waterman local alignment algorithm
- 1985: FASTA
- 1990: BLAST (basic local alignment search tool)
- 2000s: BLAST has become too slow in “genome vs. genome” comparisons - new faster algorithms evolve!
  - Pattern Hunter
  - BLAT

Slides by Rayan Chikhi
Institut Pasteur, CNRS

Original work by Heng Li

Minimap2

Two articles



Bioinformatics, 32(14), 2016, 2103–2110
doi: 10.1093/bioinformatics/btw152
Advance Access Publication Date: 19 March 2016
Original Paper

OXFORD

Sequence analysis

Minimap and miniasm: fast mapping and de novo assembly for noisy long sequences

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Medical Population Genetics, Broad Institute, Cambridge, MA 02142, USA

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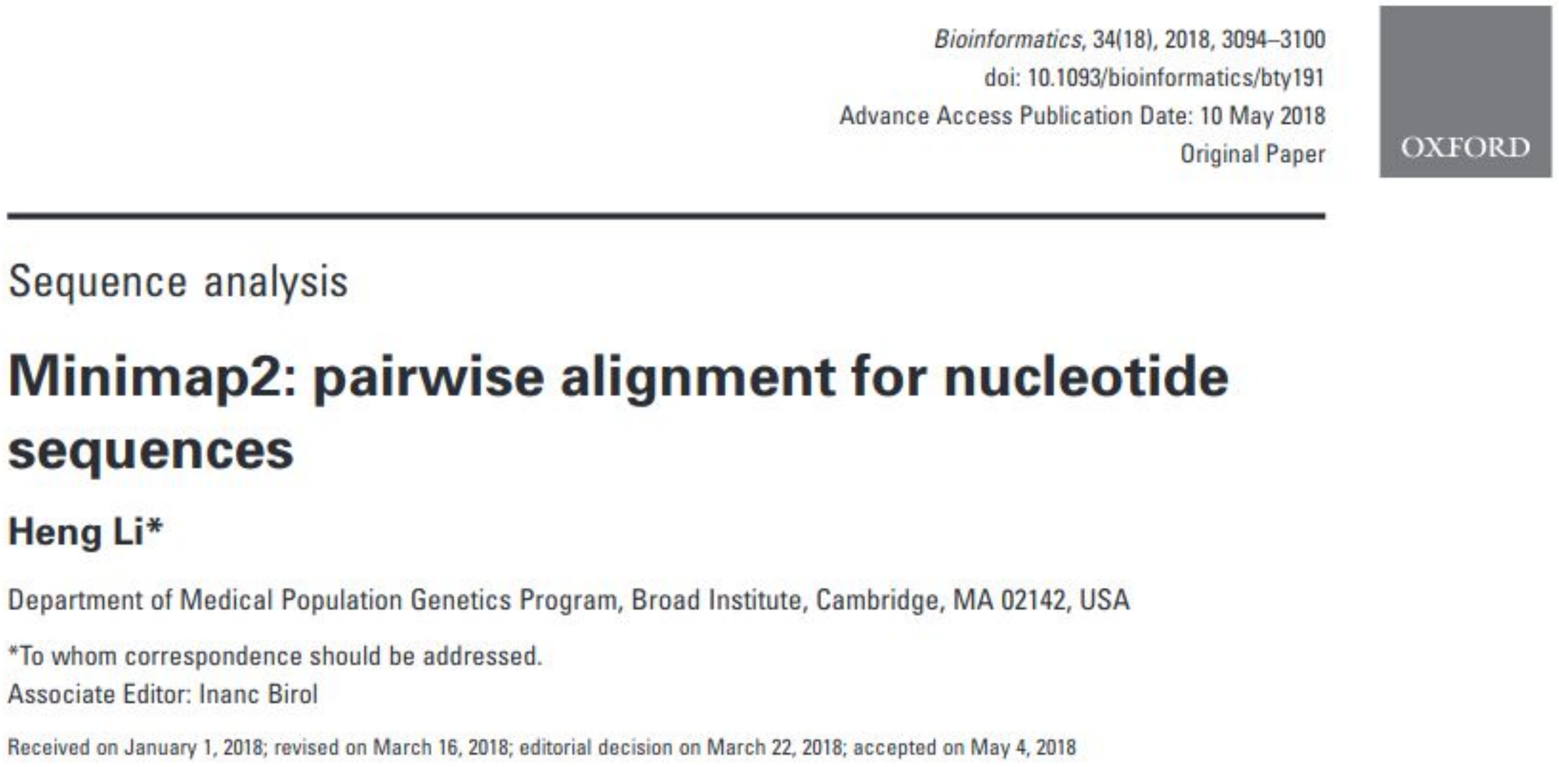
Two articles



Bioinformatics, 34(18), 2018, 3094–3100
doi: 10.1093/bioinformatics/bty191
Advance Access Publication Date: 10 May 2018
Original Paper

OXFORD

Sequence analysis

Minimap2: pairwise alignment for nucleotide sequences

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Indexing k-mers

- Index all k-mers
  - Hash tables
    - Collision-free: O(4^k) possible k-mers
    - … or many collisions
  - Other k-mer data structures (will follow)
- Minimizers:
  - "some" k-mers only
    - Reduced memory usage
  - Proposed in:
    - Roberts et al., "Reducing storage requirements for biological sequence comparison", Bioinformatics, 2004

Minimizers

- Ability to use sequence contiguity, while binning the k-mers
- Given a query length of N, all k-mers from the query will go to a different bin
- Minimizer-based binning fragments the query into ~3-4 pieces
  - Representative k-mers
  - (w,k)-minimizer: the smallest k-mer over *w* consecutive k-mers.

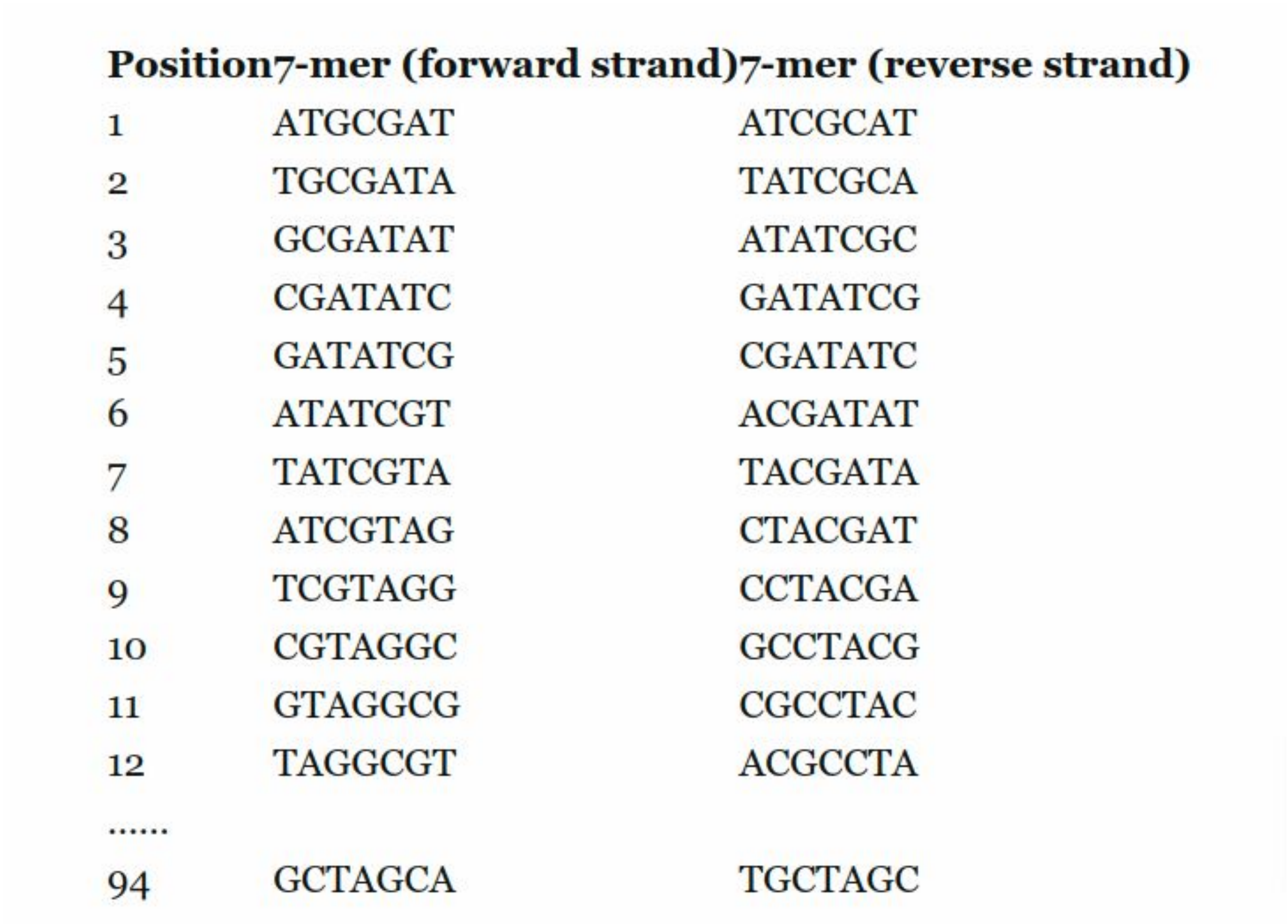
Minimizers - example

Query (length 100):

```
ATGCGATATCGTAGGCGTCGATGGAGAGCTAGATCGATCGATCTAAATCCCGATCGATTCCGAGCGCGATCAAAGCGCGATA
GGCTAGCTAAAGCTAGCA
```

Assume k=7 - for the entire query (next slide)

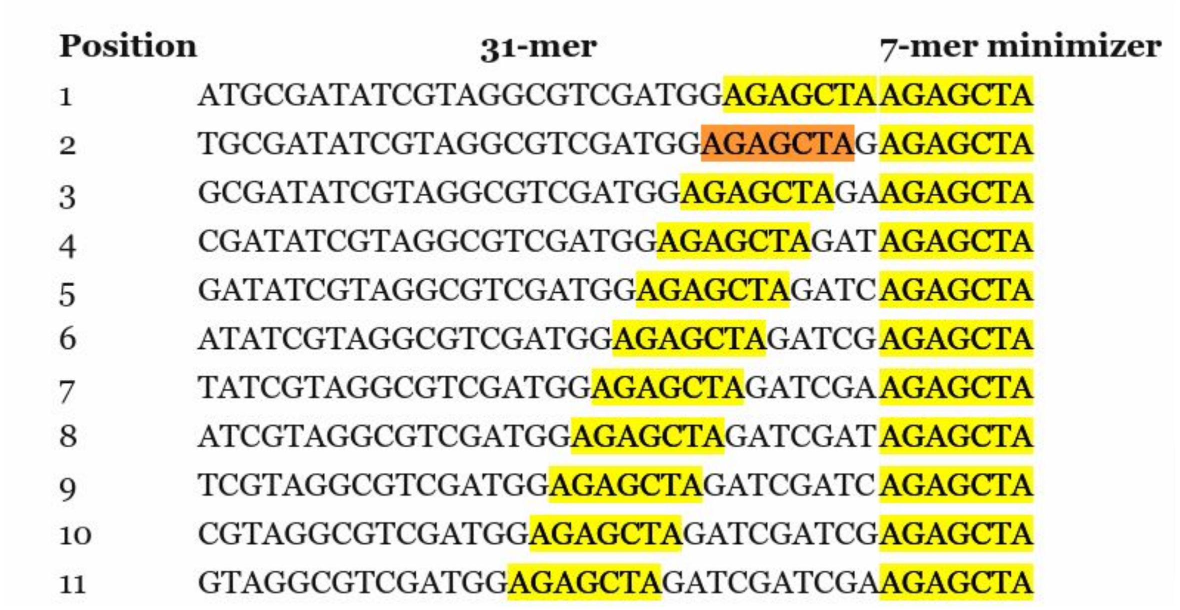
Minimizer, k=7 in the full query



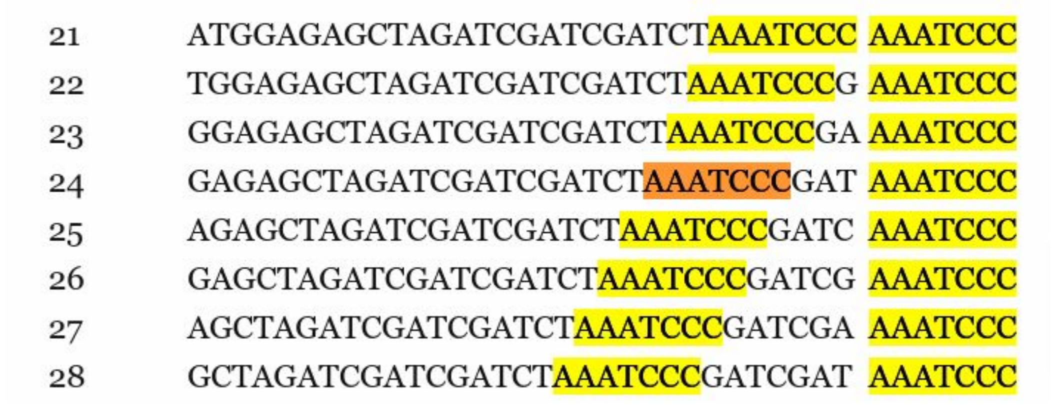
Position	7-mer (forward strand)	7-mer (reverse strand)
1	ATGCGAT	ATCGCAT
2	TGCGATA	TATCGCA
3	GCGATAT	ATATCGC
4	CGATATC	GATATCG
5	GATATCG	CGATATC
6	ATATCGT	ACGATAT
7	TATCGTA	TACGATA
8	ATCGTAG	CTACGAT
9	TCGTAGG	CCTACGA
10	CGTAGGC	GCCTACG
11	GTAGGCG	CGCCTAC
12	TAGGCGT	ACGCCTA
......		
94	GCTAGCA	TGCTAGC

188 possible 7-mers in both strands -- smallest (alphabetical): 72nd k-mer in forward: **AAAGCGC**

Minimizer, k=7, w=31



Position	31-mer	7-mer minimizer
1	ATGCGATATCGTAGGCGTCGATGGAGAGCTA	AGAGCTA
2	TGCGATATCGTAGGCGTCGATGGAGAGCTAG	AGAGCTA
3	GCGATATCGTAGGCGTCGATGGAGAGCTAGA	AGAGCTA
4	CGATATCGTAGGCGTCGATGGAGAGCTAGAT	AGAGCTA
5	GATATCGTAGGCGTCGATGGAGAGCTAGATC	AGAGCTA
6	ATATCGTAGGCGTCGATGGAGAGCTAGATCG	AGAGCTA
7	TATCGTAGGCGTCGATGGAGAGCTAGATCGA	AGAGCTA
8	ATCGTAGGCGTCGATGGAGAGCTAGATCGAT	AGAGCTA
9	TCGTAGGCGTCGATGGAGAGCTAGATCGATC	AGAGCTA
10	CGTAGGCGTCGATGGAGAGCTAGATCGATCG	AGAGCTA
11	GTAGGCGTCGATGGAGAGCTAGATCGATCGA	AGAGCTA

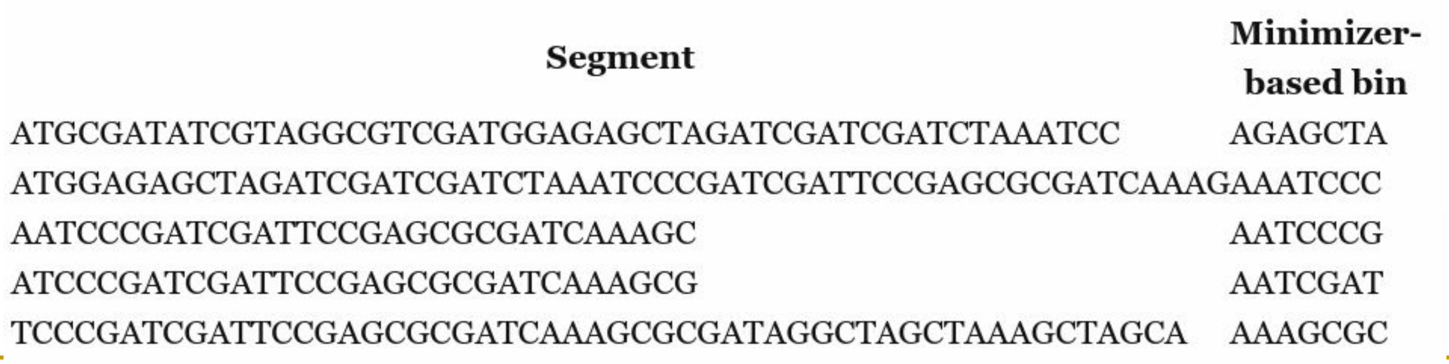


21	ATGGAGAGCTAGATCGATCGATCTAAATCCC	AAATCCC
22	TGGAGAGCTAGATCGATCGATCTAAATCCCG	AAATCCC
23	GGAGAGCTAGATCGATCGATCTAAATCCCGA	AAATCCC
24	GAGAGCTAGATCGATCGATCTAAATCCCGAT	AAATCCC
25	AGAGCTAGATCGATCGATCTAAATCCCGATC	AAATCCC
26	GAGCTAGATCGATCGATCTAAATCCCGATCG	AAATCCC
27	AGCTAGATCGATCGATCTAAATCCCGATCGA	AAATCCC
28	GCTAGATCGATCGATCTAAATCCCGATCGAT	AAATCCC

Minimizers= **AGAGCTA** and **AAATCCC**

Minimizer-based binning

- A minimizer-based binning algorithm uses the minimizer of a k-mer to bin it. The algorithm works, because each k-mer has a unique minimizer of a certain size and will therefore always go to the same bin.
- K-mer based binning: bins for all possible kmers
- In the example in the previous slides,
  - K-mer based binning: 94 bins
  - Minimizer based binning: 5 bins



Segment	Minimizer-based bin
ATGCGATATCGTAGGCGTCGATGGAGAGCTAGATCGATCGATCTAAATCC	AGAGCTA
ATGGAGAGCTAGATCGATCGATCTAAATCCCGATCGATTCCGAGCGCGATCAAAGAAATCCC	
AATCCCGATCGATTCCGAGCGCGATCAAAGC	AATCCCG
ATCCCGATCGATTCCGAGCGCGATCAAAGCG	AATCGAT
TCCCGATCGATTCCGAGCGCGATCAAAGCGCGATAGGCTAGCTAAAGCTAGCA	AAAGCGC

Minimizer-based mapping

- Minimap2
  - Collect minimizers from the reference sequence (*text*) and index in a hash table
  - For each query:
    - Collect minimizers from the query, find exact matches in the text to use as anchors
    - Identify co-linear anchors: chaining
    - Apply dynamic programming (DP) to extend from the ends of chains and to close regions between adjacent anchors in chains
      - Affine gap penalty

Heng Li, Bioinformatics, 2018

Chaining

- An anchor is a 3-tuple (x, y, w), indicating interval [x-w+1, x] on the reference matching interval [y-w+1, y] on the query.
- Given a list of anchors sorted by ending reference position x, let f(i) be the maximal chaining score up to the ith anchor in the list. f(i) can be calculated with dynamic programming

$$f(i) = \max\{\max_{i>j\geq 1}\{f(j) + \alpha(j,i) - \beta(j,i)\}, w_i\}$$

Chaining

$$f(i) = \max\{\max_{i>j\geq 1}\{f(j) + \alpha(j,i) - \beta(j,i)\}, w_i\}$$

$\alpha(j,i) = \min\{\min\{y_i - y_j, x_i - x_j\}, w_i\}$: the number of matching bases between the two anchors.

$\beta(j,i) > 0$: the gap cost

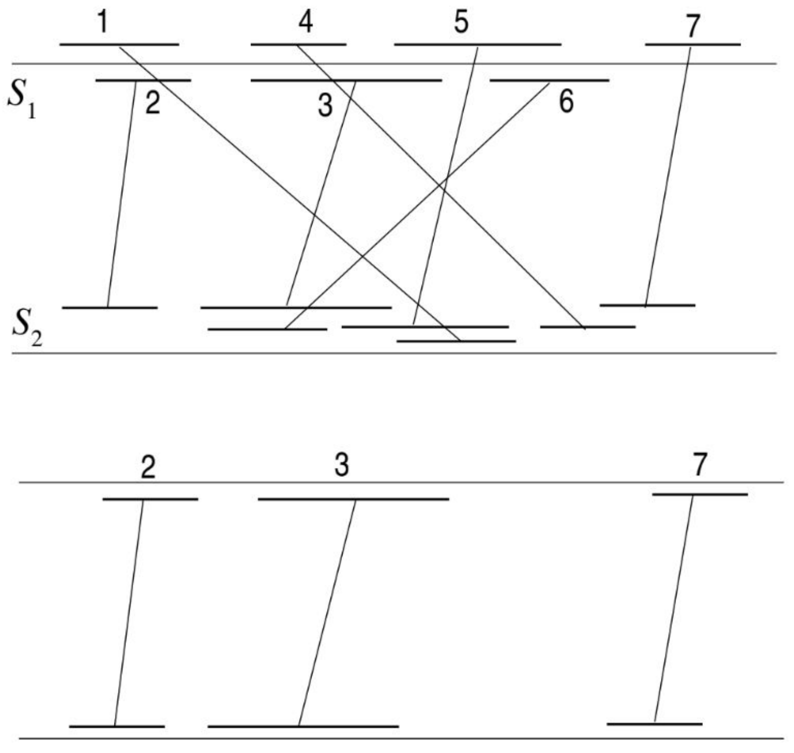
G: max dist between anchors

$$\beta(j,i) = \begin{cases} \infty, & \text{if } y_j \geq y_i. \\ \infty, & max\{y_i - y_j, x_i - x_j\} > G. \\ \gamma_c((y_i - y_j) - (x_i - x_j)) & \text{otherwise} \end{cases}$$

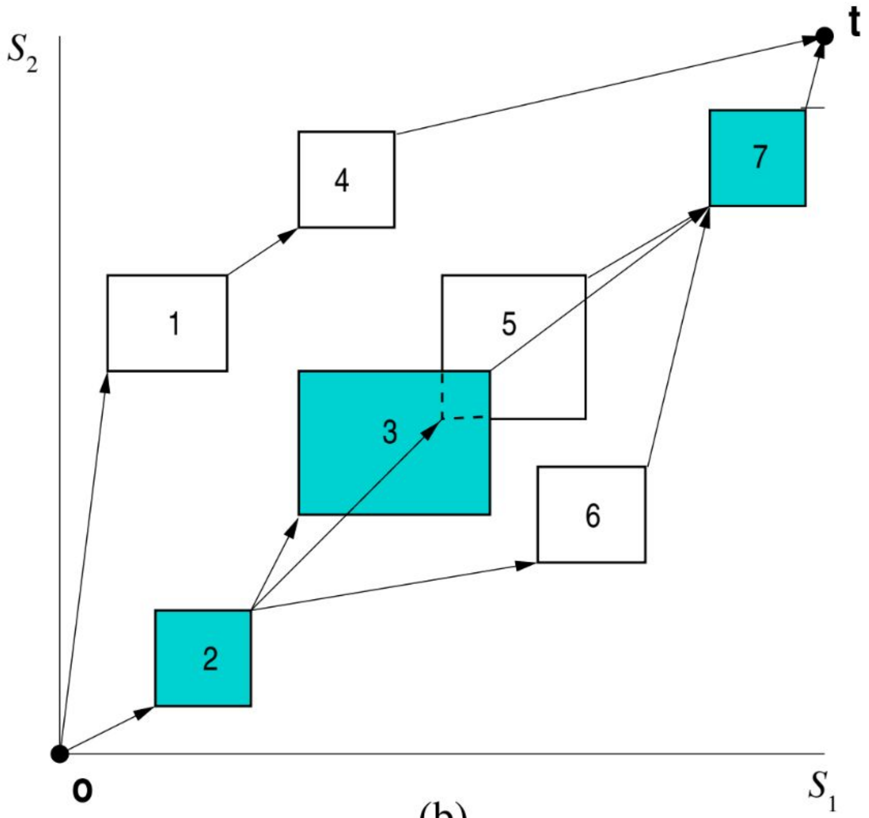
$$\gamma_c(l) = \begin{cases} 0.01 \cdot \overline{w} \cdot |l| + 0.5 \log_2 |l| & (l \neq 0) \\ 0 & (l = 0) \end{cases}$$

w is the average seed length

Chaining



(a)



(b)

MAXIMAL UNIQUE MATCHES

MUMs

- A *maximal unique match* of two strings *S* and *T* is a substring *X* that occurs exactly once in both *S* and *T* and cannot be extended to the left or to the right without losing one of the occurrences.

$X=s_i s_{i+1}\ldots s_{i+k-1}$, $X=t_j t_{j+1}\ldots t_{j+k-1}$, and $s_{i-1}\neq t_{j-1}$, $s_{i+k}\neq t_{k+1}$

- To detect MUMs of two strings *S* and *T*, is simple
  - How?
  - And *d* strings (S^1, S^2, …, S^d)?
    - in O(|Σ|+n) time where $n = \Sigma_{i=1}^{d} |S^i|$

MUMmer: whole genome alignment

- Whole mammalian genomes are ~3 Gb
  - Human chromosome 1 is ~250 Mb.
- Whole genome alignments using Smith-Waterman is therefore infeasible
- MUMmer (v1 1999, v2 2002, v3 2004) tries to solve this problem using MUMs as *anchors*
  - GPU accelerated version: MUMmerGPU (2013)
  - Combination of: suffix trees, longest increasing subsequences, and Smith-Waterman

Delcher et al., Nucleic Acids Research, 1999

MUMmer

1. Find MUMs in Genomes A and B
2. Sort the matches found in the MUM alignment, and extract the longest possible set of matches that occur in the same order in both genomes.
   a. LIS of a sequence of integers.
   b. An ordered MUM alignment that provides an easy way to scan the alignment from left to right.
3. Close the gaps in the alignment by performing local identification of large inserts, repeats, small mutated regions, tandem repeats and substitutions
4. Output the alignment, including all the matches in the MUM alignment as well as the detailed alignments of regions that do not match exactly

Delcher et al., Nucleic Acids Research, 1999

MUMmer

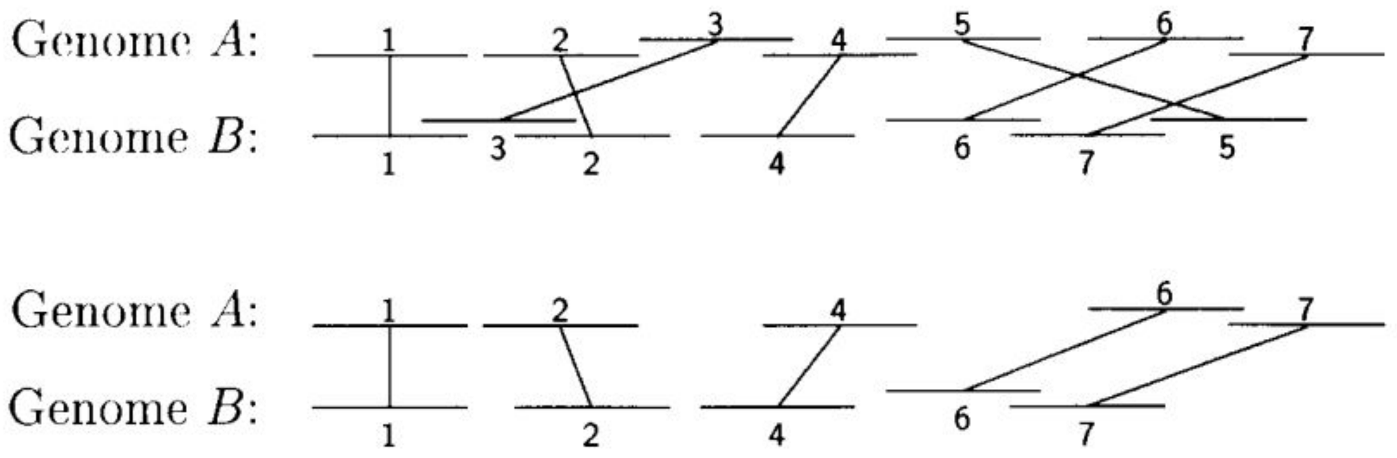
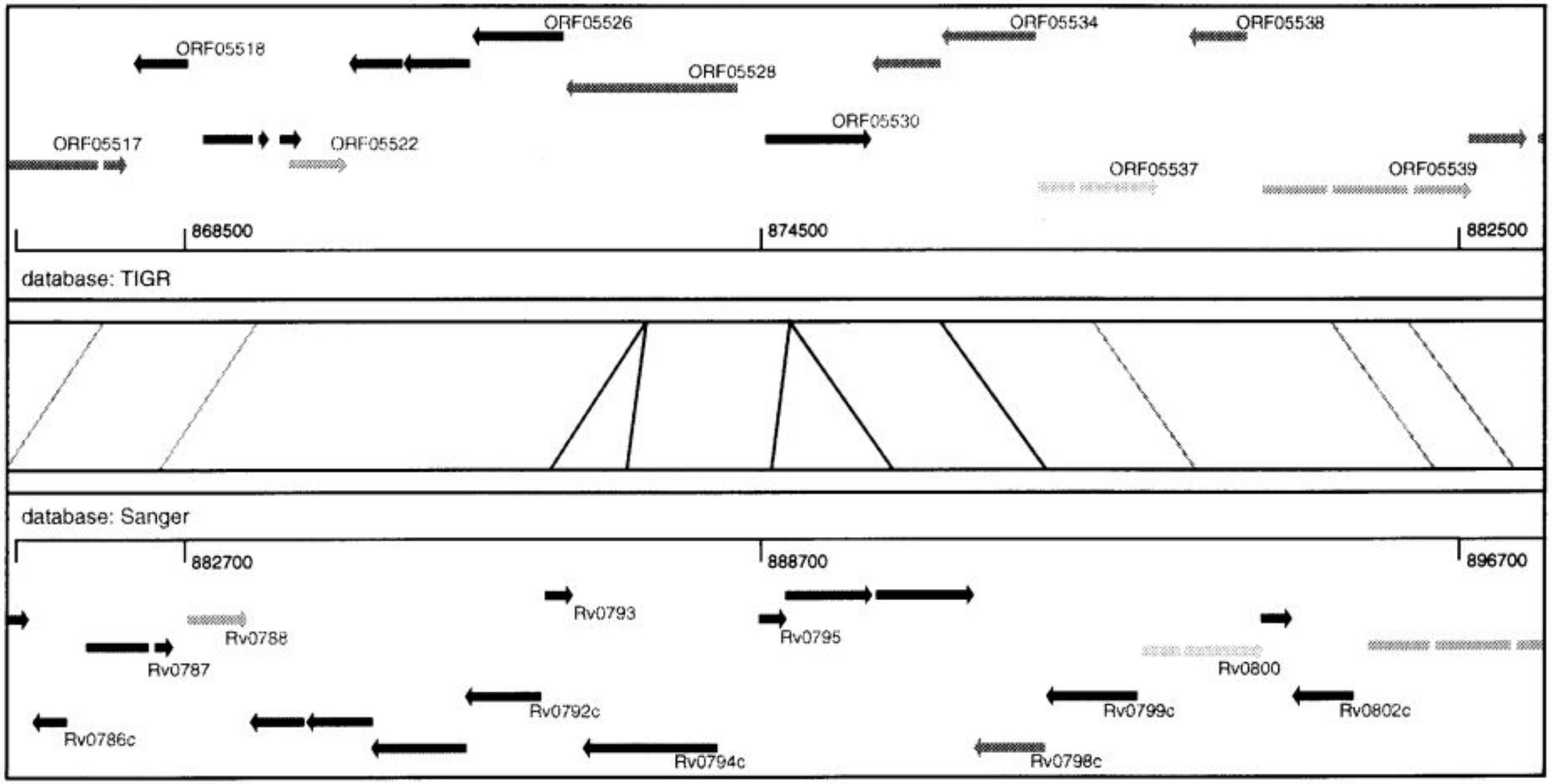


Figure 3. Aligning Genome *A* and Genome *B* after locating the MUMs. Each MUM is here indicated only by a number, regardless of its length. The top alignment shows all the MUMs. The shift of MUM 5 in Genome *B* indicates a transposition. The shift of MUM 3 could be simply a random match or part of an inexact repeat sequence. The bottom alignment shows just the LIS of MUMs in Genome *B*.

Delcher et al., Nucleic Acids Research, 1999

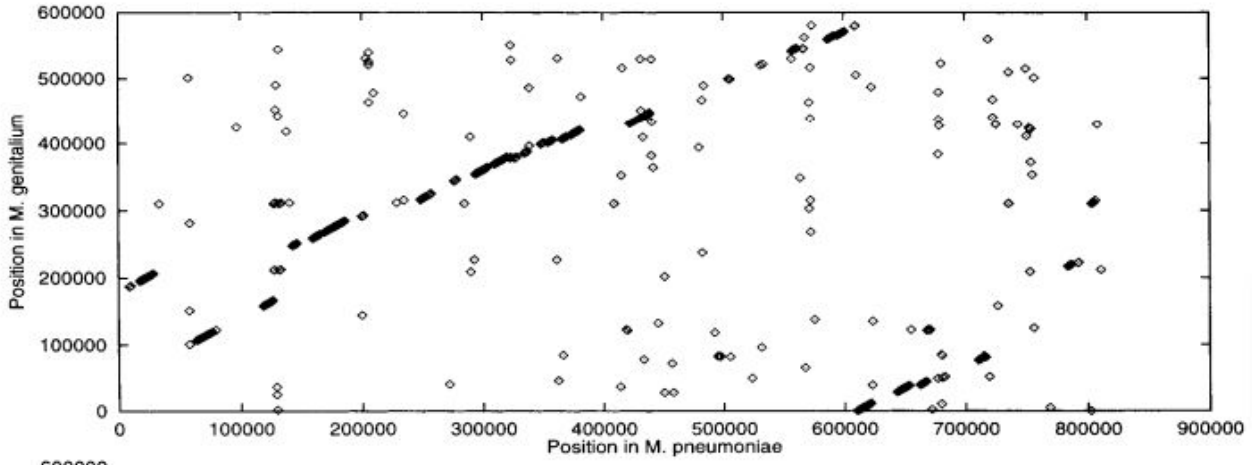
MUMmer: M. tuberculosis strains



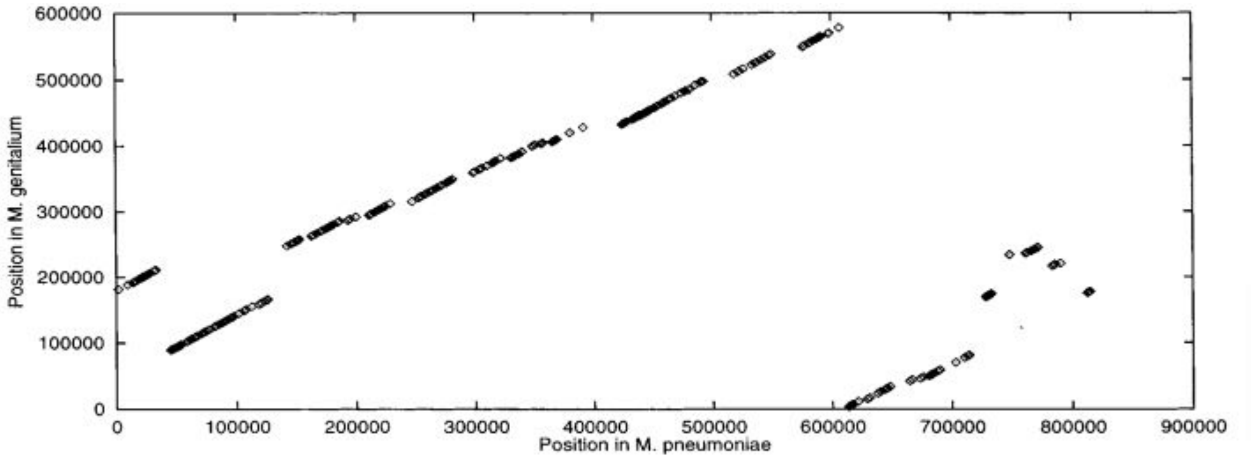
Delcher et al., Nucleic Acids Research, 1999

MUMmer vs FASTA

FASTA



MUMmer



Delcher et al., Nucleic Acids Research, 1999

MUMs for MSA

- If the sequences to align are similar, MUMs can be used as anchors for MSA
- Input: d sequences $S^1, \ldots, S^d$ of length $n_1, \ldots, n_d$
- Find max-length MUM for all sequences, ***α***
  - This occurs exactly once in each S^i at position j_i, for $1 \leq i \leq d$, that you can use to split the set into two independent parts:

$$S^1_{1\ldots j_1}, S^2_{1\ldots j_2}, \ldots S^d_{1\ldots j_d} \text{ and } S^1_{j_1+|\alpha|\ldots n_1}, S^2_{j_2+|\alpha|\ldots n_2}, \ldots S^d_{j_d+|\alpha|\ldots n_d}$$

- Apply the same recursively until sufficiently short sequences are obtained, suitable for MSA

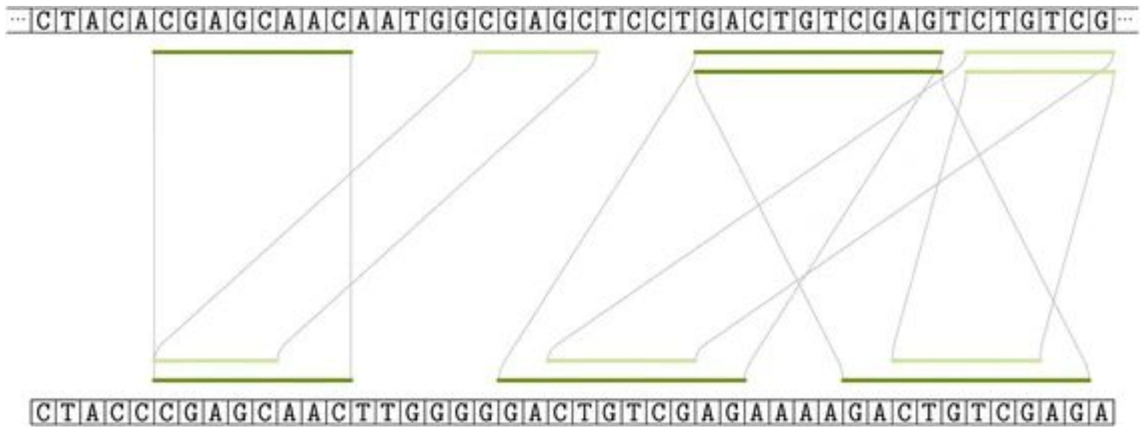
MAXIMAL EXACT MATCHES

MEMs

- MEMs: exact matches between two strings that cannot be extended in either direction towards the beginning or end of two strings without allowing for a mismatch.
- Relaxation of MUMs, removing the uniqueness requirement
- The only constraint is the minimum length, *L*
- All MEMs @ low memory $\rightarrow$ bidirectional BWT index

BWA-MEM

- Seed-and-extend strategy for aligning billions of short queries to a large text (e.g., genome)
- Seeds -> Super-Maximal Exact Matches
  - SMEMs: MEMs that are not contained in other MEMs



···CTACACGAGCAACAATGGCGAGCTCCTGACTGTCGAGTCTGTCG···
CTACCCGAGCAACTTGGGGGACTGTCGAGAAAAGACTGTCGAGA

Vyverman et al. BMC Bioinformatics 2015

Heng Li, arXiv, 2013

BWA-MEM

1. Seeding: SMEMs: each query position the longest match covering the position
2. Chaining: greedy chaining algorithm, done while seeding
    a. Discard short chains
3. Extension: banded affine-gap alignment