Computational Aspects in Gene Order Studies

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Comparative genomics

Comparative genomics is applied with several goals in mind:

- Comparative gene finding, annotation
- Binding site prediction, phylogenetic footprinting
- Genome alignment
- Correlated expression
- Conserved gene neighborhood
- Rearrangement studies

Comparative genomics “at a higher level”

Concentrate on large scale layout of the genomes:

- Study genomes based on their *gene order*.
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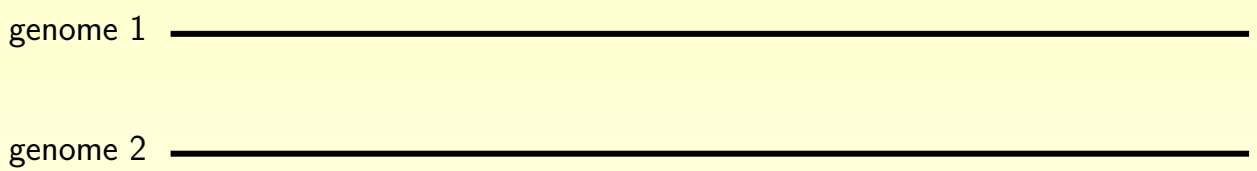

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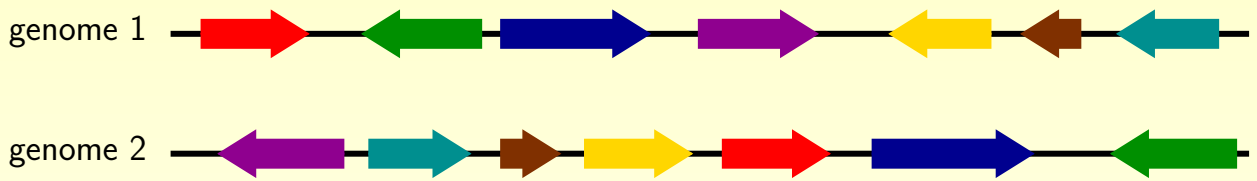

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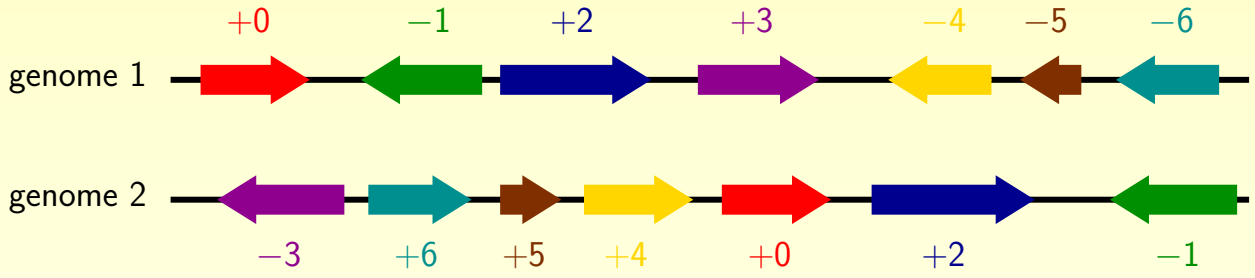

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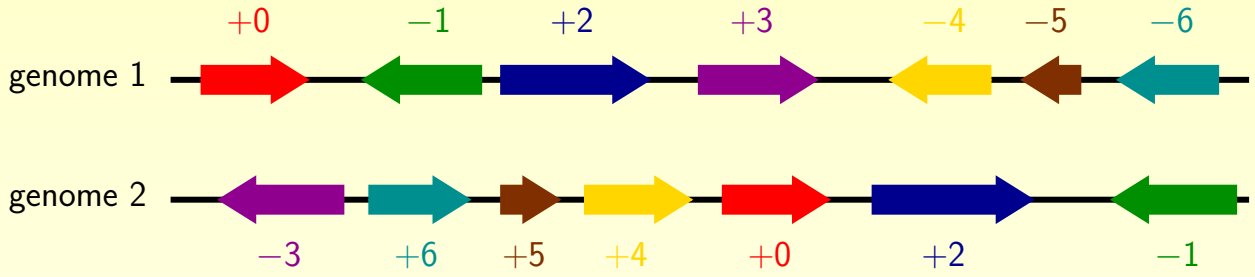

More formally:

- Genes = (signed) elements from the set $N = \{0, \ldots, n\}$.
- Corresponding (*orthologous*) genes get the same number.
- Genomes = (signed) permutations of N.

Protein function prediction

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- Literature based:
  - Natural language processing

Genome-based gene function prediction

Comparative genomics meets functional genomics.

Idea: Genes that repeatedly cluster together in phylogenetically remotely related genomes are functionally associated:

- interacting proteins
- proteins of the same protein complex
- enzymes of the same metabolic pathway

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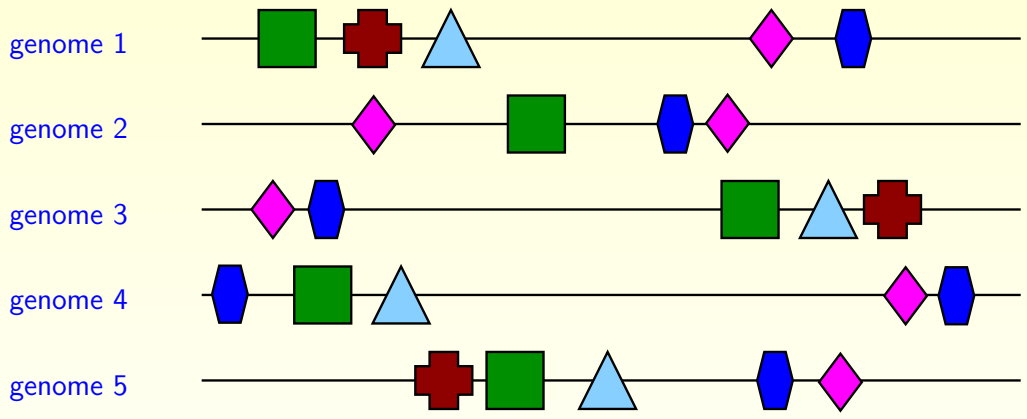

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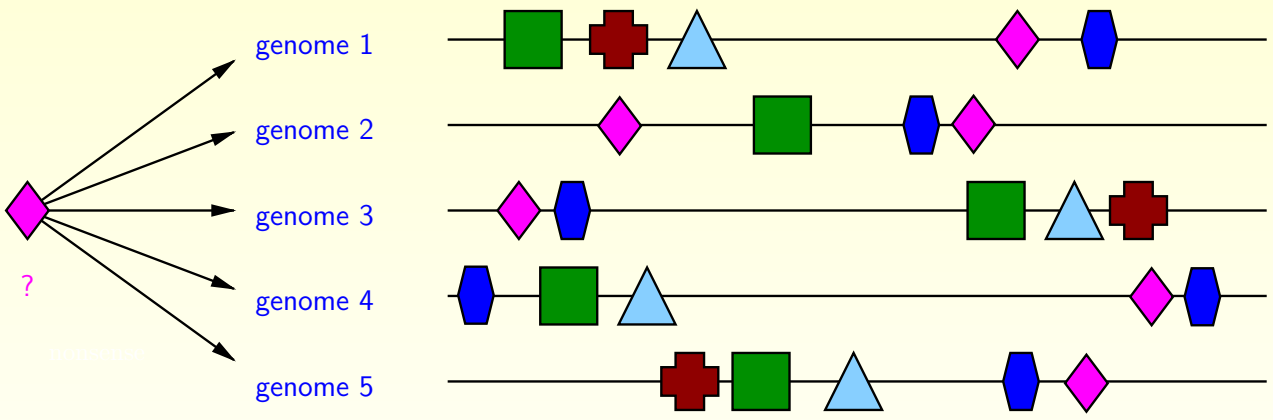

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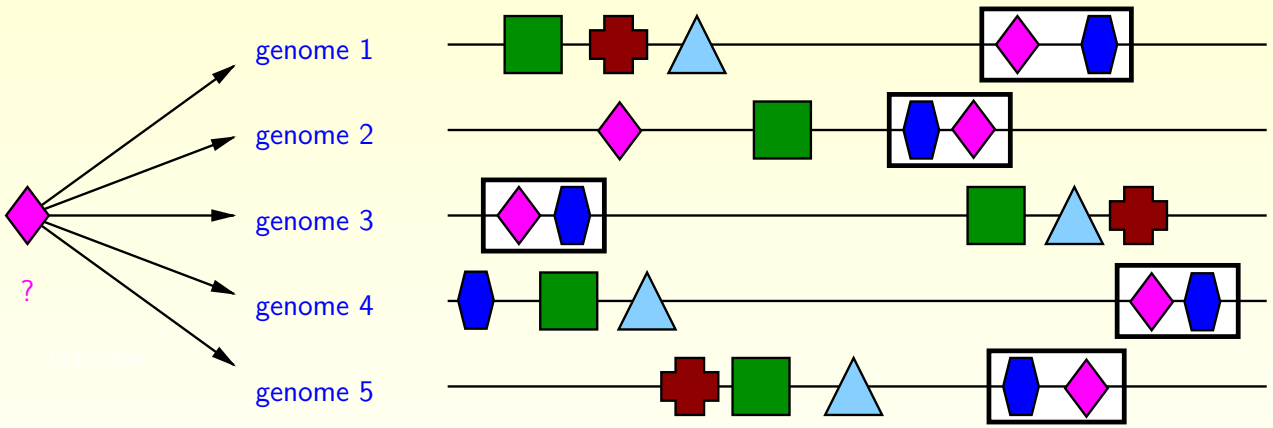

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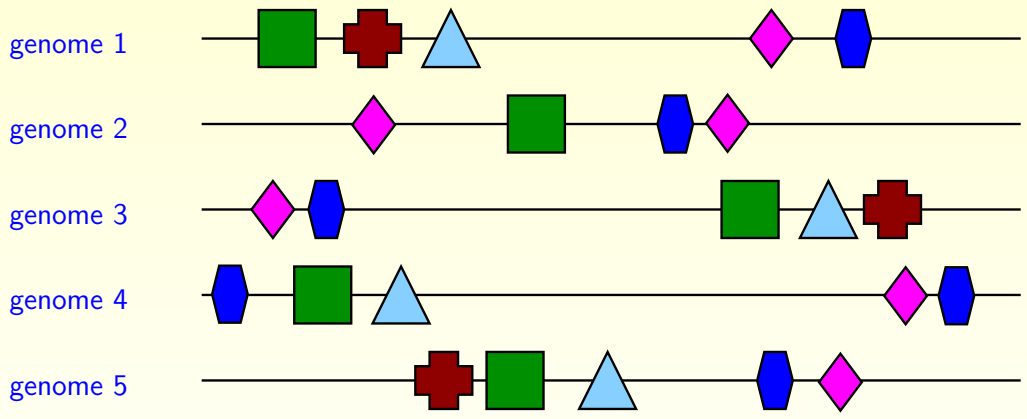

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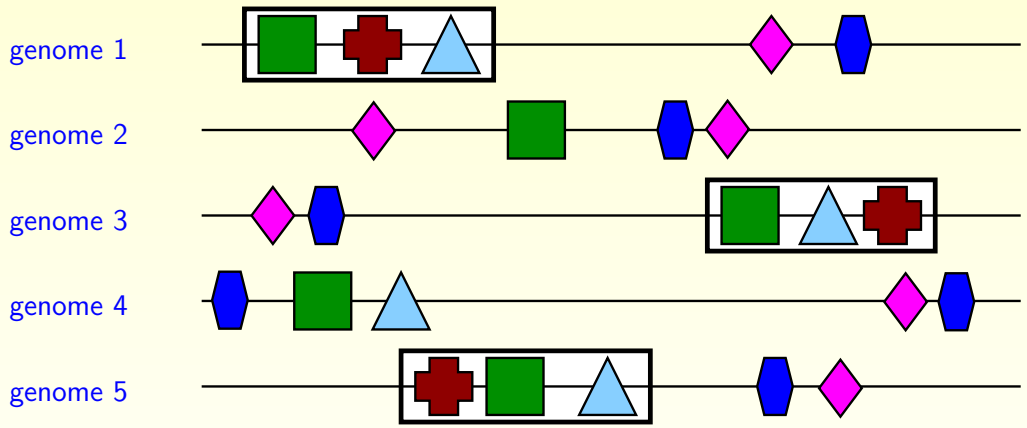

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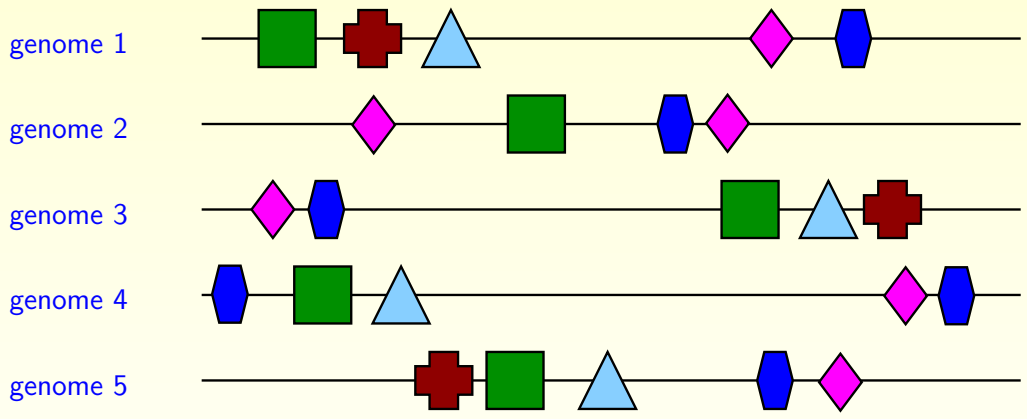

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Marcotte *et al.*: Detecting protein function and protein-protein interactions from genome sequences. *Science*, 1999.

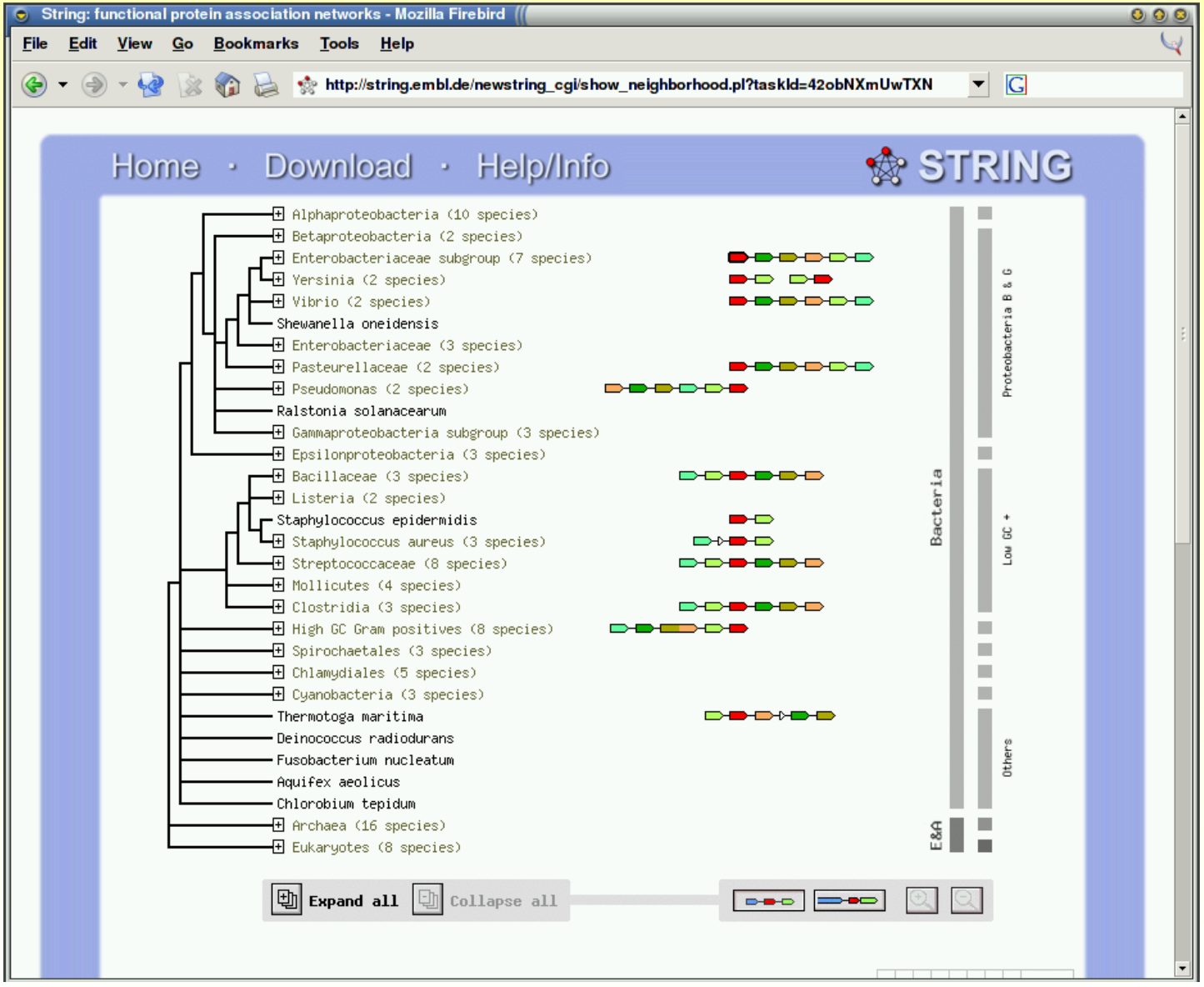
Overbeek *et al.*: The use of gene clusters to infer functional coupling. *PNAS*, 1999.

Snel *et al.*: STRING: A web-server to retrieve and display the repeatedly occurring neighbourhood of a gene, *NAR*, 2000.

Zheng *et al.*: Phylogenetic detection of conserved gene clusters in microbial genomes, *BMC Bioinformatics*, 2005.

STRING Web server (Snel et al., 2000)

http://string.embl.de/



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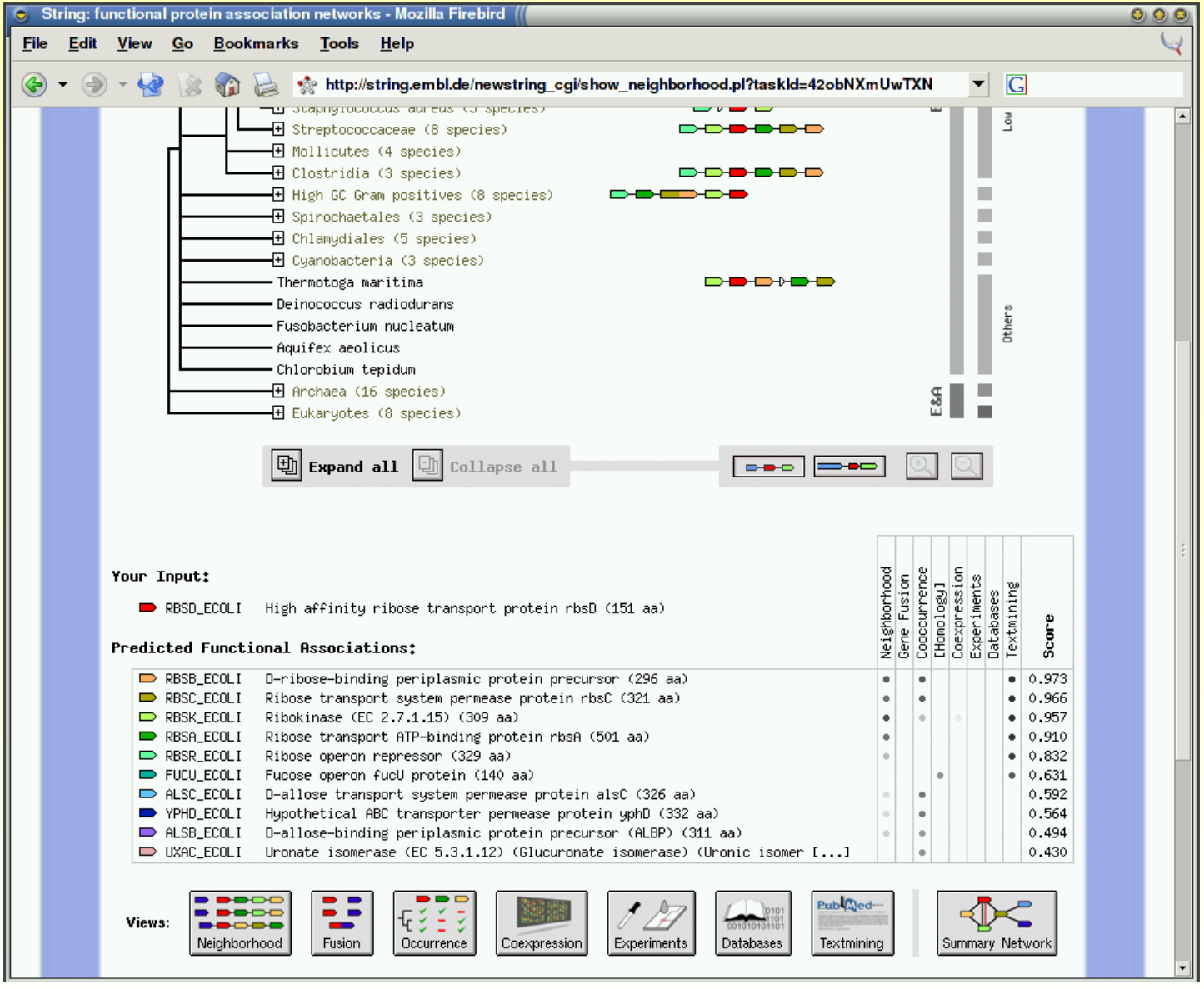
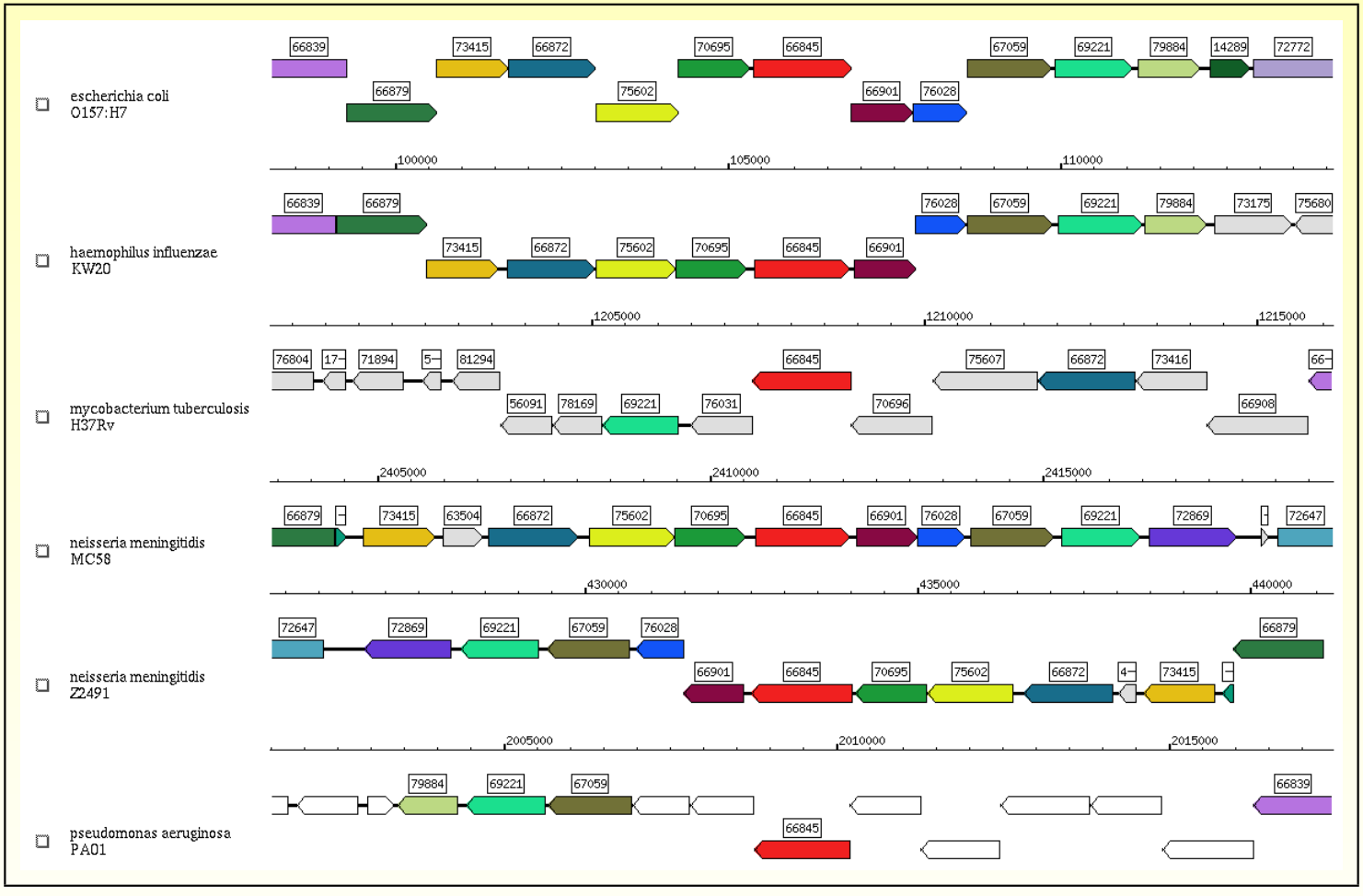
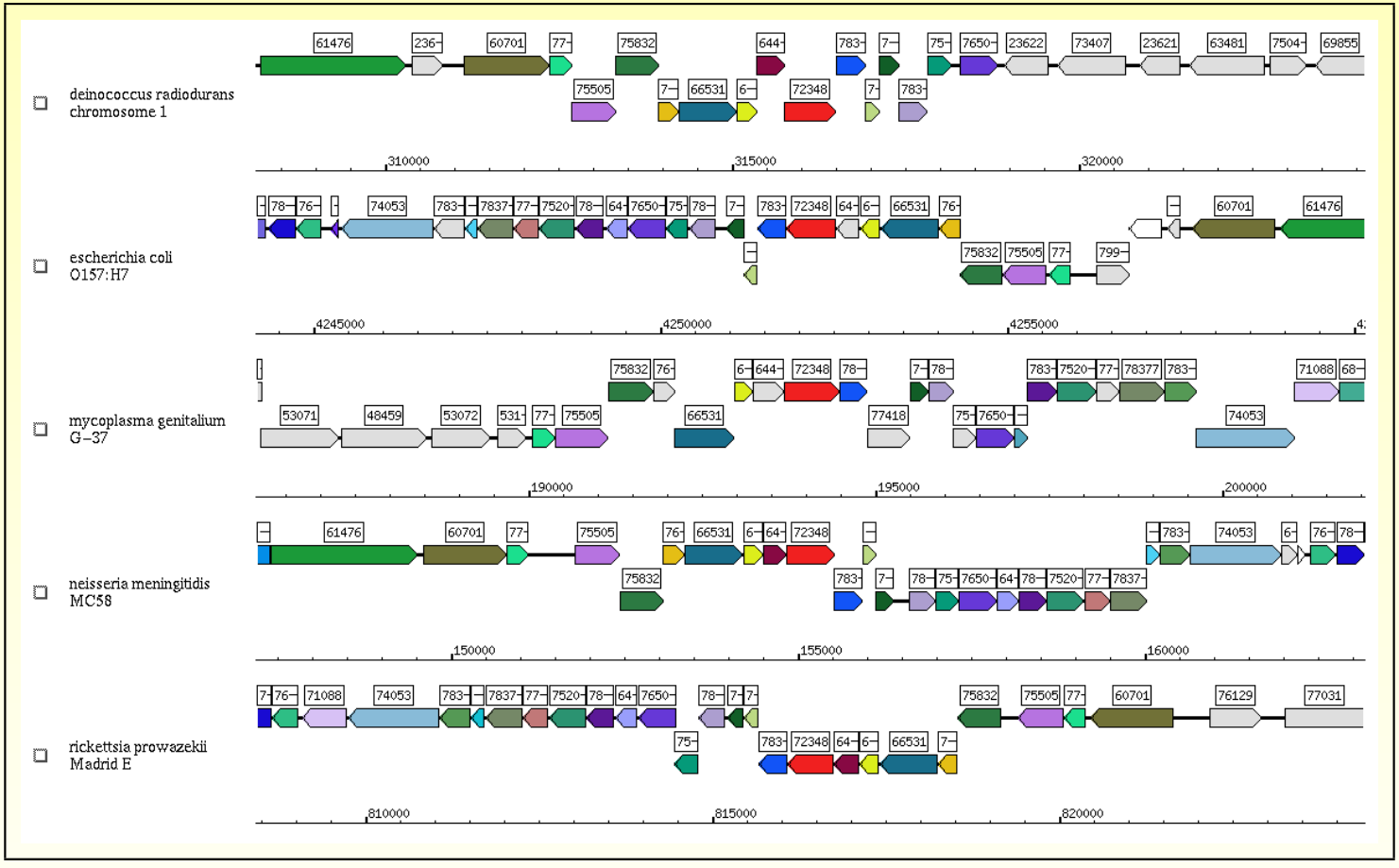


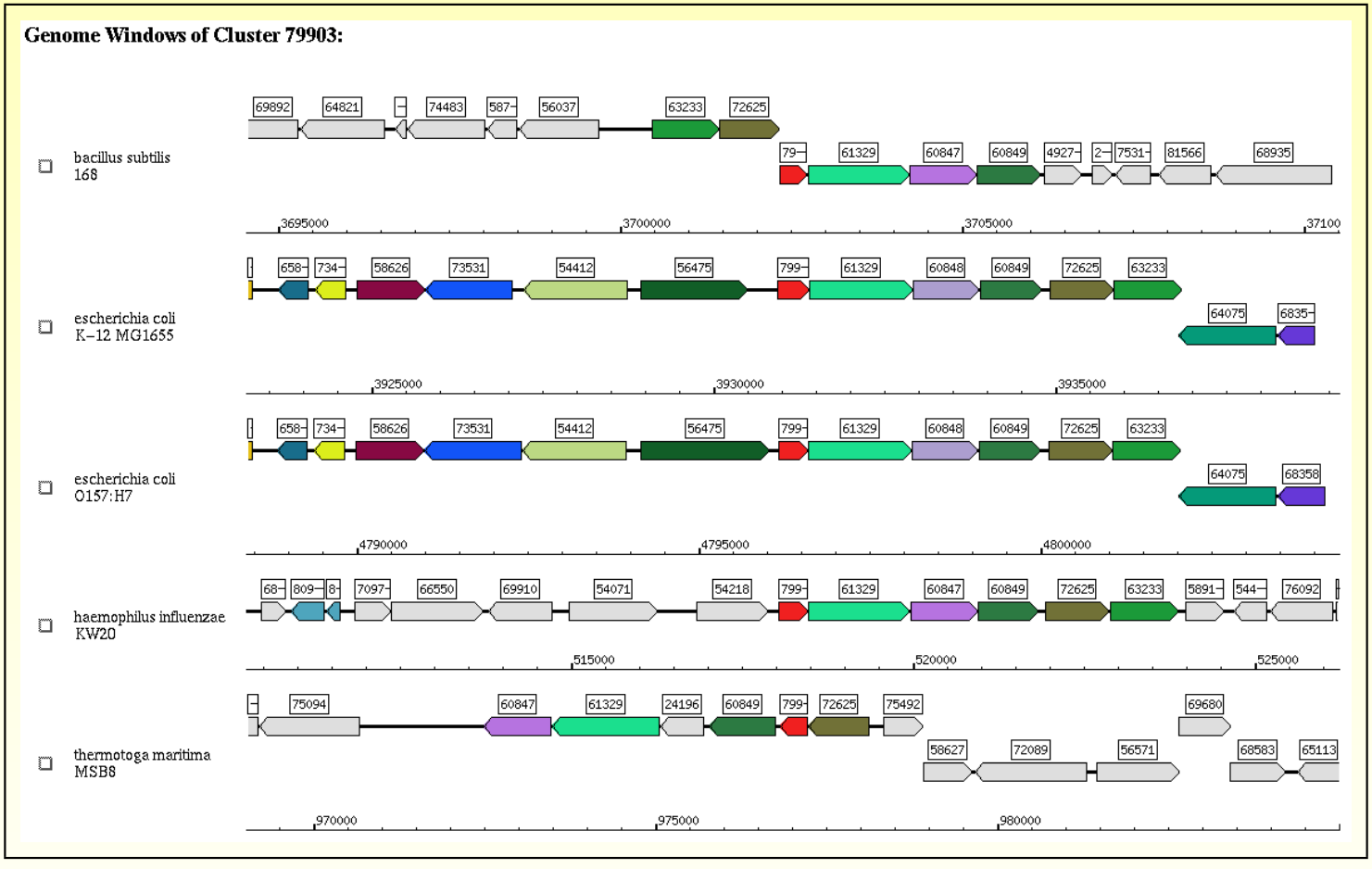
Genome Windows: DCW cluster (division and cell wall)



Genome Windows: Ribosomal Super Operon



Genome Windows: Ribose ABC Transporter



Formalization of gene clusters: common intervals

Given permutations (genomes) $\pi_1, \pi_2, \ldots, \pi_k$ of the numbers (genes) $0, 1, \ldots, n$, find subsets of numbers that occur contiguously in all permutations.

π_1	0	1	2	3	4	5	6	7
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Algorithms:

- Uno & Yagiura, *Algorithmica* 2000:
  Find all common intervals of 2 permutations in $\mathcal{O}(n + |\text{output}|)$ time.
- Heber & JS, *CPM* 2001:
  Find all common intervals of $k \geq 2$ permutations in $\mathcal{O}(kn + |\text{output}|)$ time.

Finding all common intervals of two permutations π_1 and π_2

Let $1 \leq x \leq y \leq n$.

Notation: $\pi([x, y]) := \{\pi(x), \pi(x+1), \ldots, \pi(y)\}$

Definitions:
$$l(x, y) := \min \pi_2([x, y])$$
$$u(x, y) := \max \pi_2([x, y])$$
$$f(x, y) := u(x, y) - l(x, y) - (y - x)$$

Example:

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Simple algorithm: For all $1 \leq x \leq y \leq n$ test if $f(x, y) = 0$.

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Analysis: $\mathcal{O}(n^2)$ time.

Finding all common intervals of two permutations π_1 and π_2

Uno & Yagiura, 2000:

Perform the test $f(x, y) = 0$ not for all pairs (x, y).

Definition:

For given x, call a value of $y > x$ *wasteful*, if and only if for all $x' \leq x$:

$$f(x', y) > 0.$$

Lemma:

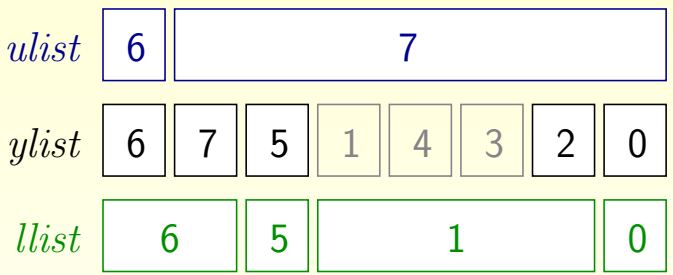
For fixed x, $f(x, y)$ increases monotonically for the non-wasteful indices y $(> x)$.

Algorithm (Idea):

- x runs in right-to-left direction through a doubly linked list *ylist* that initially contains the entries of π_2.
- In each step, the entries of wasteful indices y $(> x)$ are removed.
- Test for the remaining $y > x$ in *ylist* from left to right if $f(x, y) = 0$.

Algorithm RC (Uno & Yagiura)

- Removal of wasteful indices from *ylist* is done by means of two additional lists *llist* and *ulist* that implement the functions l and u.
- The elements of *llist* and *ulist* are maximal intervals of *ylist* with the same smallest resp. largest element.



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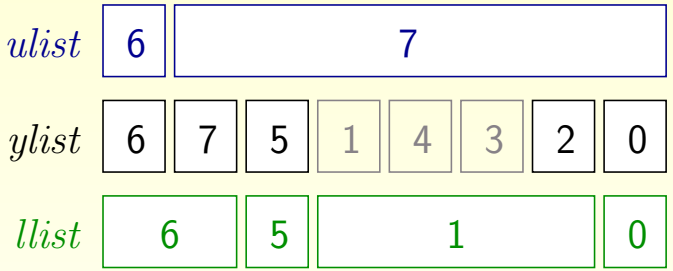

Analysis:
$\mathcal{O}(n + |\text{output}|)$ time, $\mathcal{O}(n)$ space.

Finding all common intervals of $k \geq 2$ permutations

Obvious generalization:

Given k permutations $\pi_1, \pi_2, \ldots, \pi_k$.

For $j = 2, 3, \ldots, k$ compute the common intervals of π_1 and π_j.

Output all intervals that are found in all of these comparisons.

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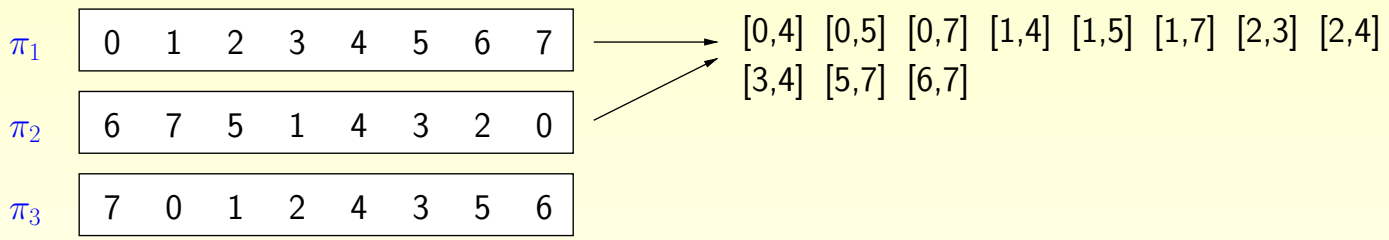

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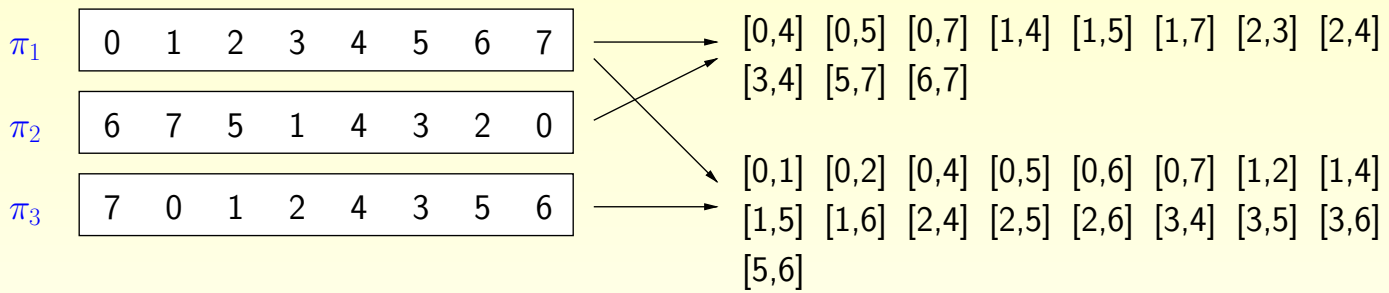

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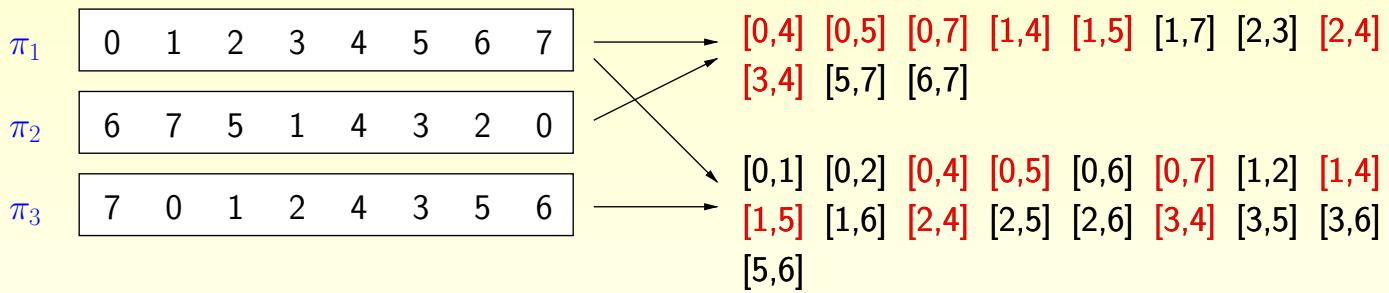

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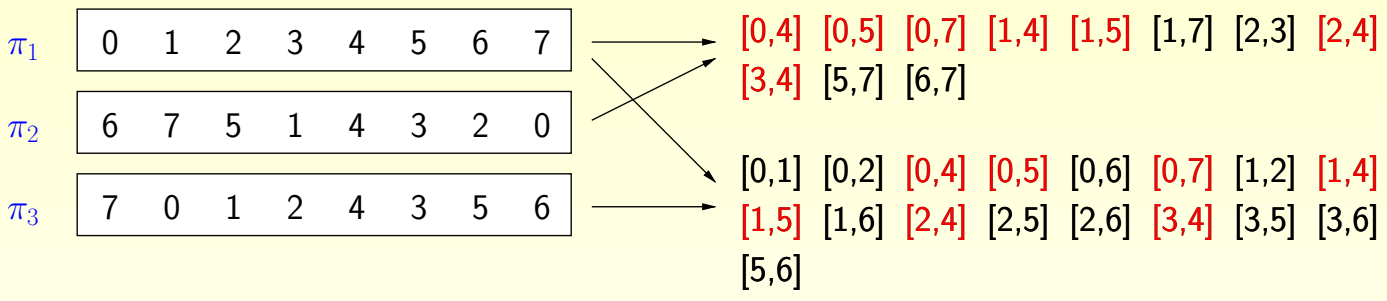


Analysis:

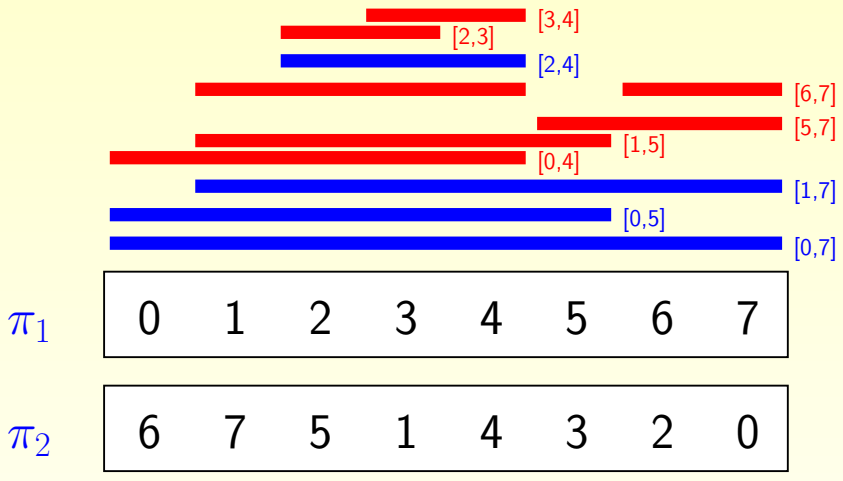
$\mathcal{O}(kn + \sum |K_i|)$ time

where K_i = the number of common intervals of π_1 and π_i.

Irreducible Intervals

Goal: An algorithm with output-dependent time complexity $\mathcal{O}(kn + |\text{output}|)$.

Observation: Common intervals form *"chains"* of non-trivially overlapping intervals.



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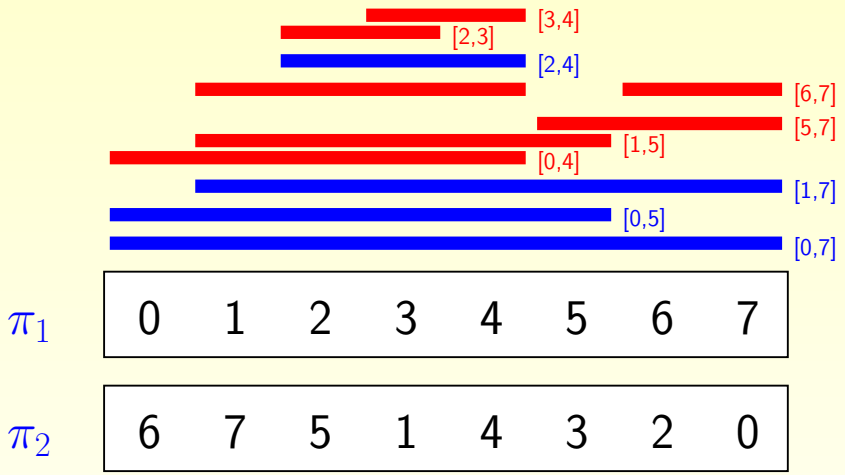


Definition:

A common interval c is reducible if there exists a non-trivial chain that generates c, otherwise it is irreducible.

Properties of irreducible intervals

Lemma:

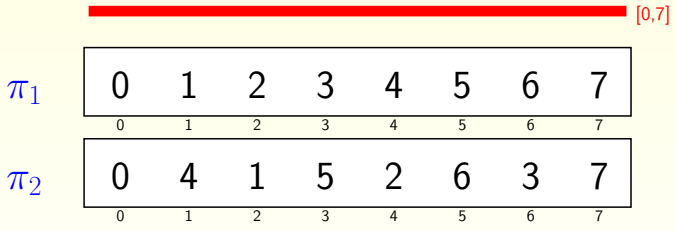
The subchains of all the maximal chains of irreducible intervals generate exactly all common intervals.

Theorem:

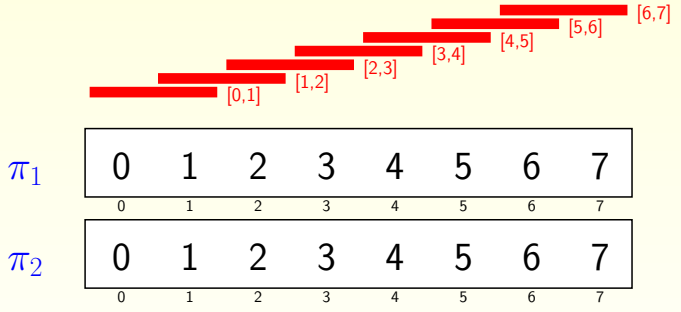
For the number of irreducible intervals K the following holds:

$$1 \leq K \leq n - 1$$

Example:



$K = 1$

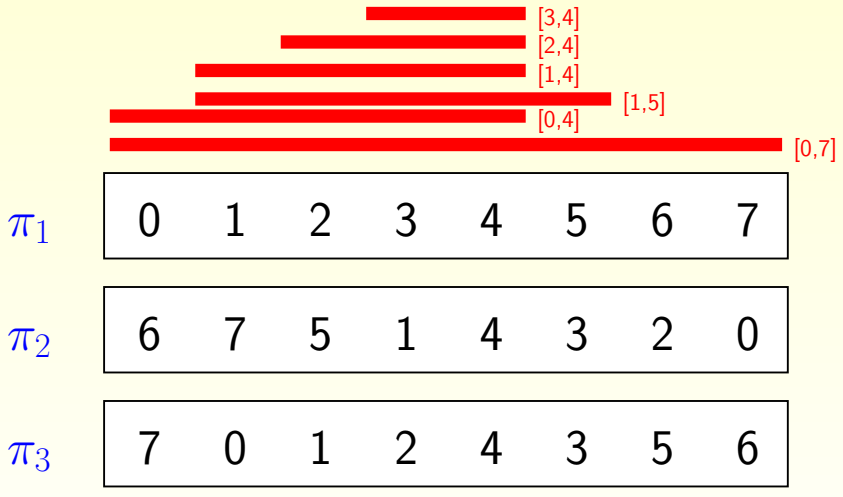


$K = n - 1$

Finding all common intervals of k $\geq$ 2 permutations

Algorithm:

- Find the set of all irreducible intervals.
- Partition this set into maximal chains of non-trivially overlapping intervals.
- For each such chain generate all subchains: the common intervals.



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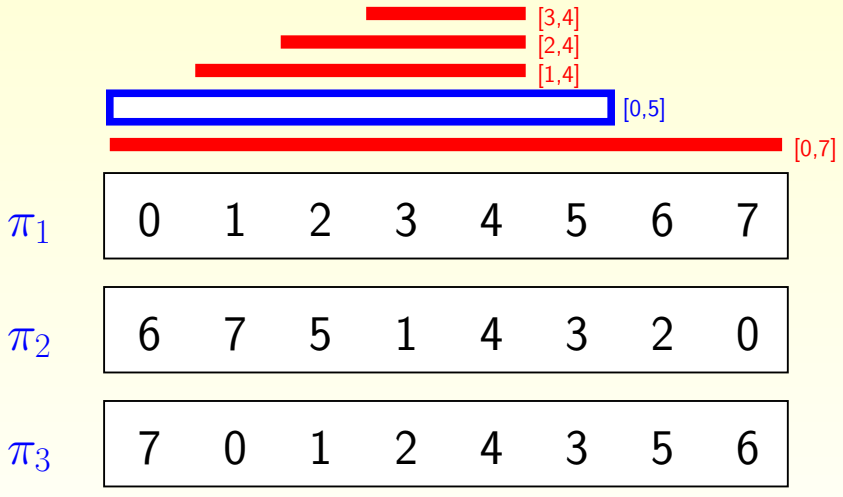

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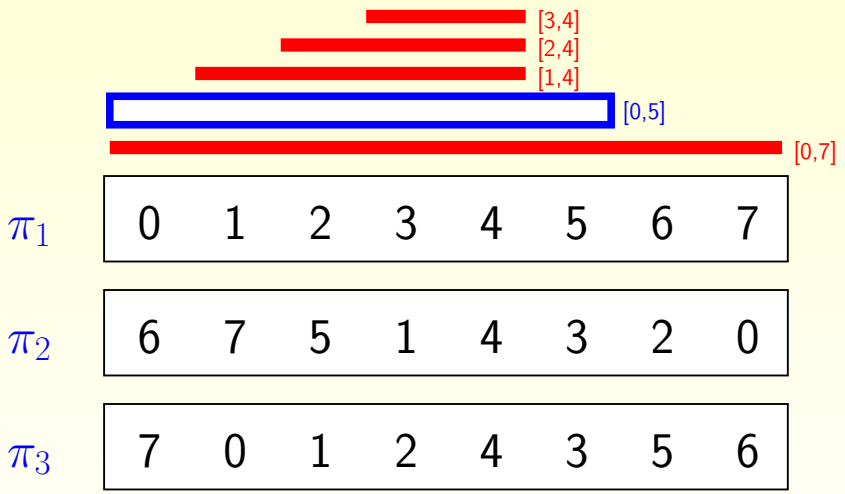
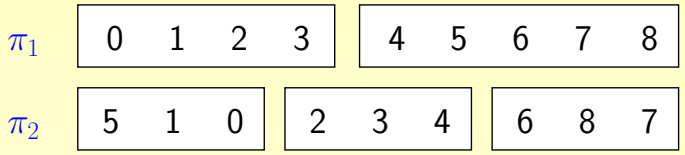


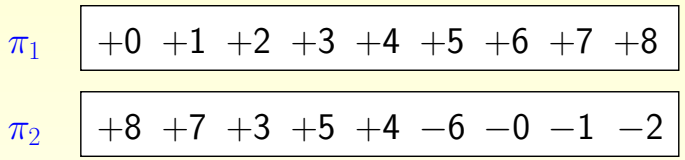
Analysis: $\mathcal{O}(kn + |\text{output}|)$ time, $\mathcal{O}(n)$ additional space

More realistic genome models

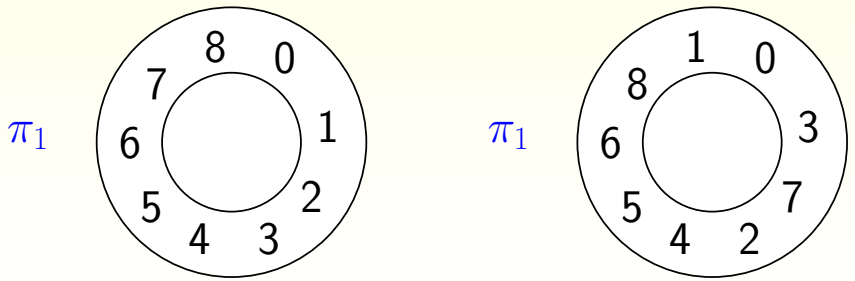
1. Genomes of higher organisms often have more than one chromosome
   $\Rightarrow$ *multichromosomal permutations*



2. Genes of a cluster should lie on the same DNA strand
   $\Rightarrow$ *signed permutations*



3. Bacterial, archaeal, and mitochondrial DNA is often circular
   $\Rightarrow$ *circular permutations*



Further extensions of the model

Generalization

- Allow paralogous genes (gene families)

Relaxation:

- Common intervals do not have to be contained in all genomes
- Not each gene has always to occur

Other applications

- Inverse of *Consective Arrangement Problem*
- Candidates for *Subtour Exchange Crossover* in genetic algorithms
- Model-free distance for phylogenetic analyses

Inclusion of paralogous genes

Problem:
In case of *duplicated genes*, it is difficult to assign correct orthologous gene pairs.
Possibly *the* ortholog does not even exist.

Consequence:
Do not distinguish between paralogous gene copies.

New model:
Use the same element (number) more than once for paralogous copies of genes.
$\longrightarrow$ genomes are modeled as *sequences* instead of permutations.

Formal model

Given: k sequences $\mathcal{S} = (S_1, S_2, \ldots, S_k)$ over an alphabet Σ.

Common interval:
a subset $C \subseteq \Sigma$ whose elements occur contiguously in each $S_l \in \mathcal{S}$.

Goal:
Find all maximal occurrences of common intervals in $\mathcal{S}$.

Example:

S_1	3	1	2	3	1	5	2	6
S_2	4	3	5	5	5	1	4	2	2
S_3	7	5	1	5	3	6	5	

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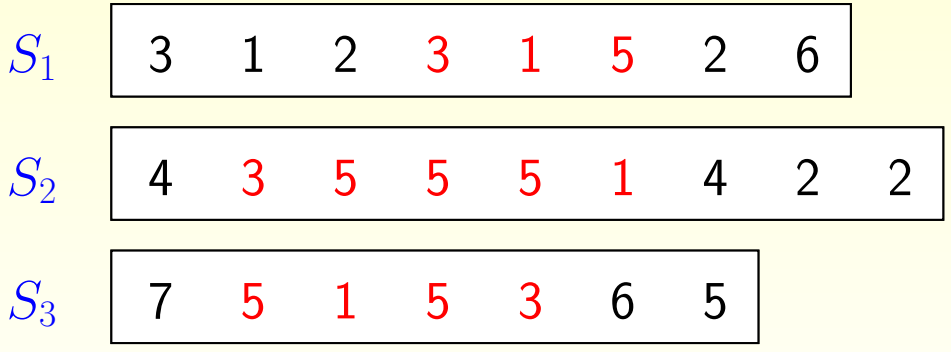

Common intervals: {1,3,5}

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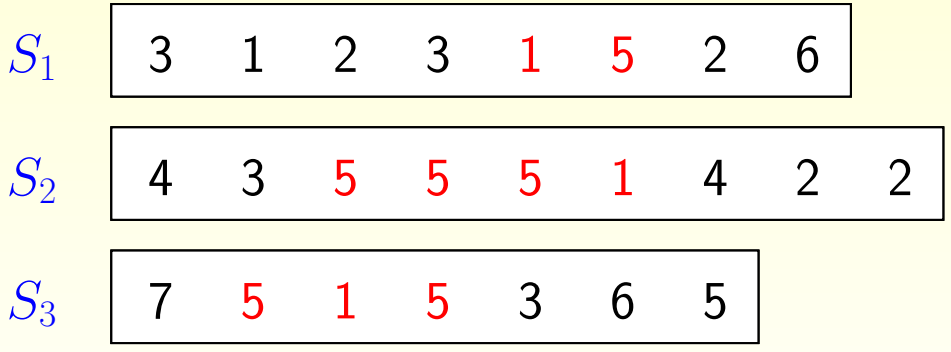

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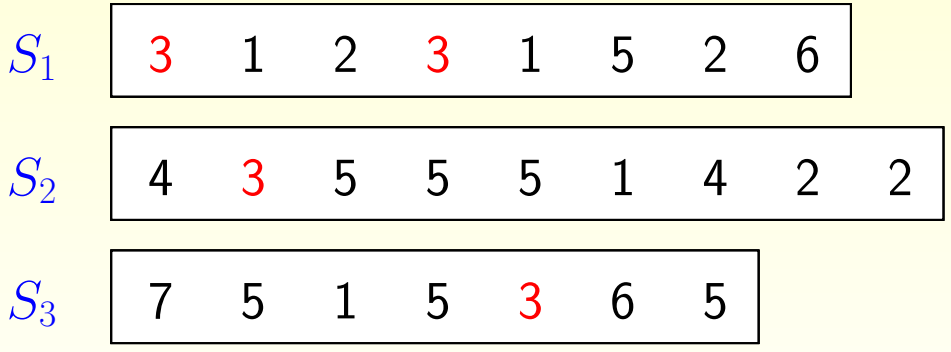

Common intervals: {1,3,5} {1,5} {5} {3}

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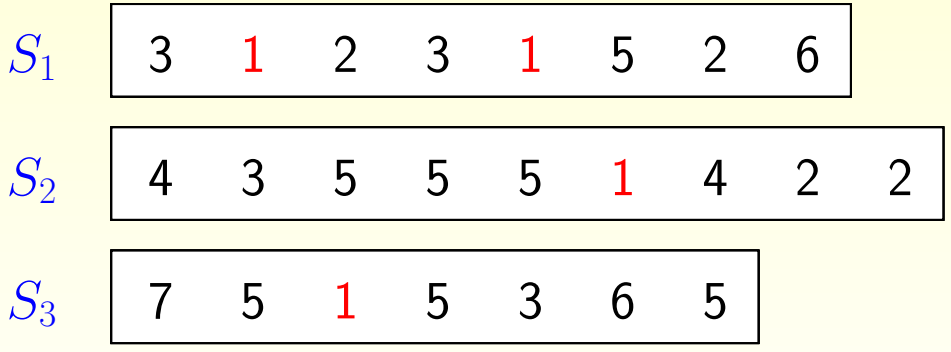

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An elementary algorithm for two sequences

Preprocessing: compute two tables for $S_1 = (3, 1, 2, 3, 1, 5, 2, 6)$:

$POS[1] = 2, 5$
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$NUM(i, j)$:

$i \backslash j$	0	1	2	3	4	5	6	7
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1		1	2	3	3	4	4	5
2			1	2	3	4	4	5
3				1	2	3	4	5
4					1	2	3	4
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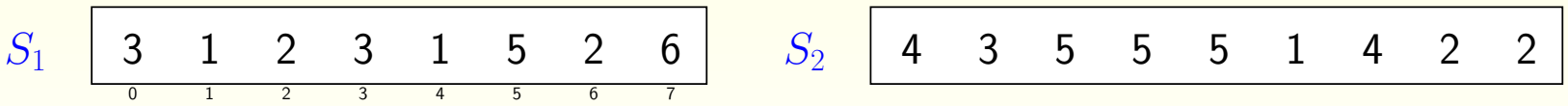
Connecting Intervals Algorithm (Schmidt & JS, *CPM 2004*):
While reading S_2, mark in S_1 the observed characters and track maximal intervals of marked characters.



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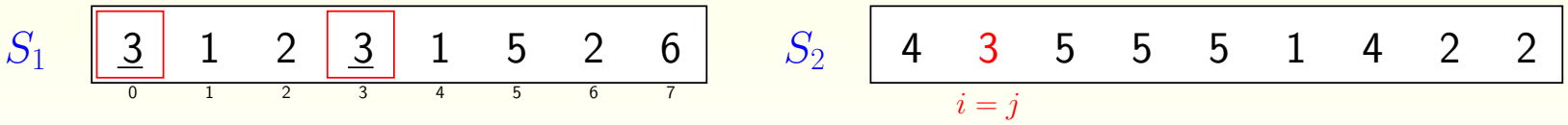

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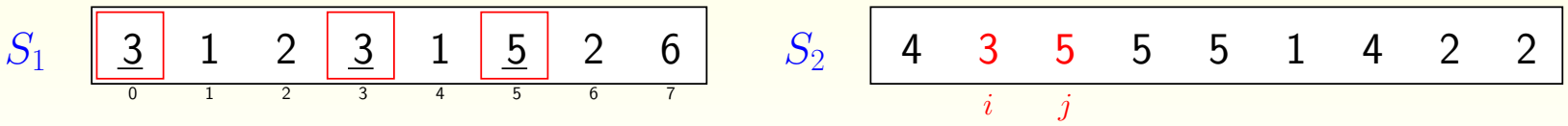

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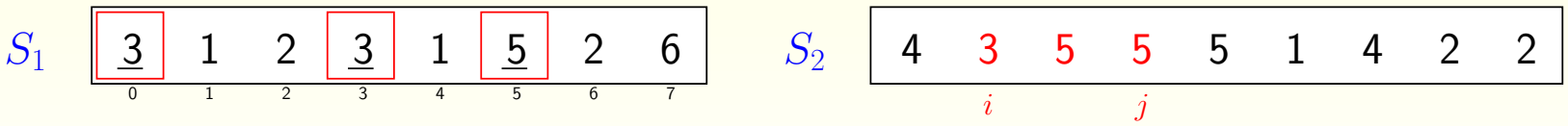

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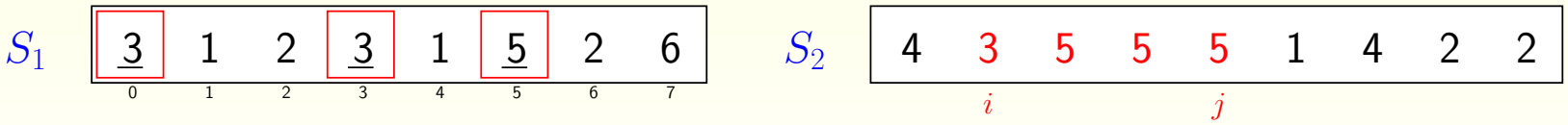

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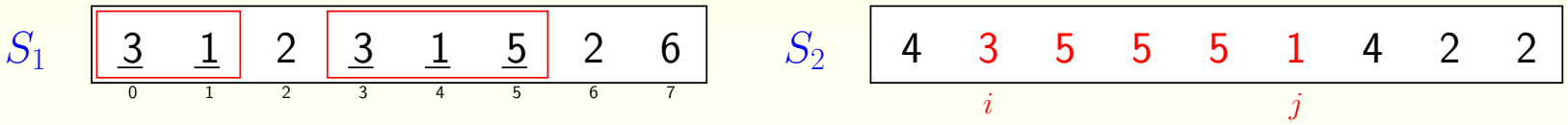

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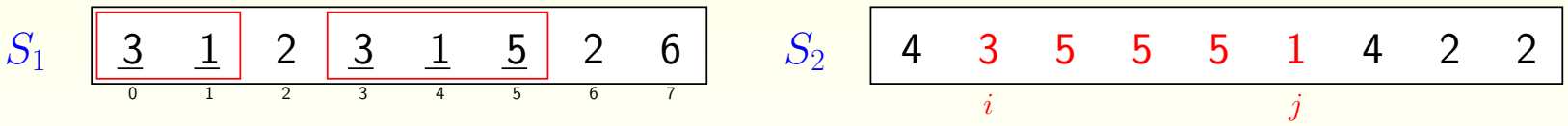


Analysis: $\mathcal{O}(n^2)$ time and space.

More algorithms

Space reduction:

- A different algorithm based on work by Didier (*WABI*, 2003) finds all common intervals of two sequences in $\mathcal{O}(n^2)$ time and $\mathcal{O}(n)$ space.

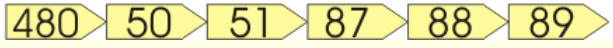
More than two sequences:

- Find all common intervals in k sequences in $\mathcal{O}(kn^2)$ time and space.
- Find all common intervals that appear in at least k' out of k given sequences in $\mathcal{O}(k(1+k-k')n^2)$ time and $\mathcal{O}(kn^2)$ space.

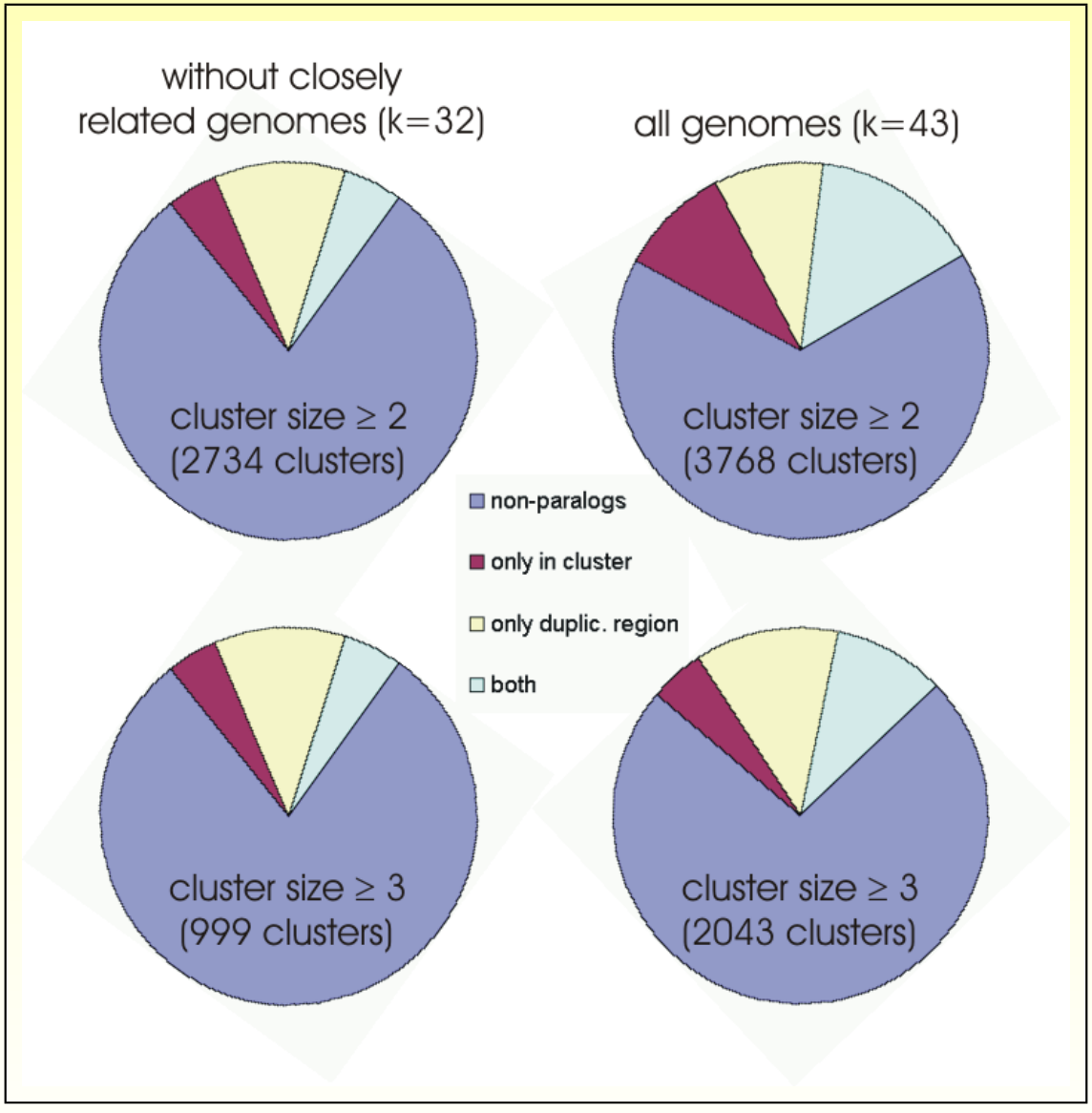
Experimental results. Data source: COG

Aquifex aeolicus complete genome - 0..1551335
1529 proteins

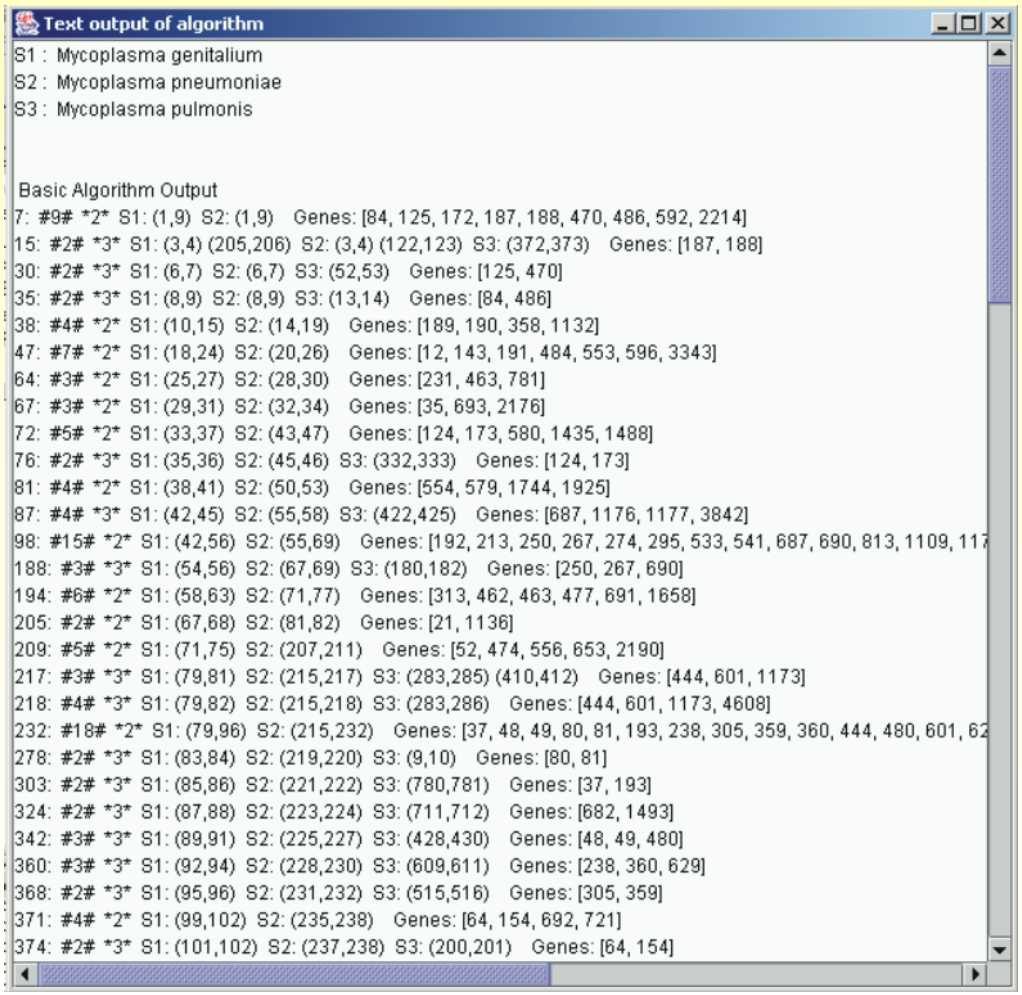
Location	Strand	Length	PID	Synonym	Code	COG	Product
1..2100	+	699	15605613	fusA	J	COG0480	elongation factor EF-G
17..3334	+	405	15605614	tufA1	J	COG0050	elongation factor EF-Tu
46..3660	+	104	15605615	rpsJ	J	COG0051	ribosomal protein S10
3665..4390	+	241	15605616	rplC	J	COG0087	ribosomal protein L03
4387..4986	+	199	15605617	rplD	J	COG0088	ribosomal protein L04
4990..5301	+	103	15605618	rplW	J	COG0089	ribosomal protein L23
5313..6227	+	304	15605619	rplB	J	COG0090	ribosomal protein L02
6340..6900	+	186	15605620	rpsS	J	COG0185	ribosomal protein S19
7018..7314	+	98	15605621	rplV	J	COG0091	ribosomal protein L22



Experimental results. Application to 43 bacterial genomes



Experimental results. Graphical inspection of gene clusters: GECKO (bibiserv.techfak.uni-bielefeld.de/gecko)



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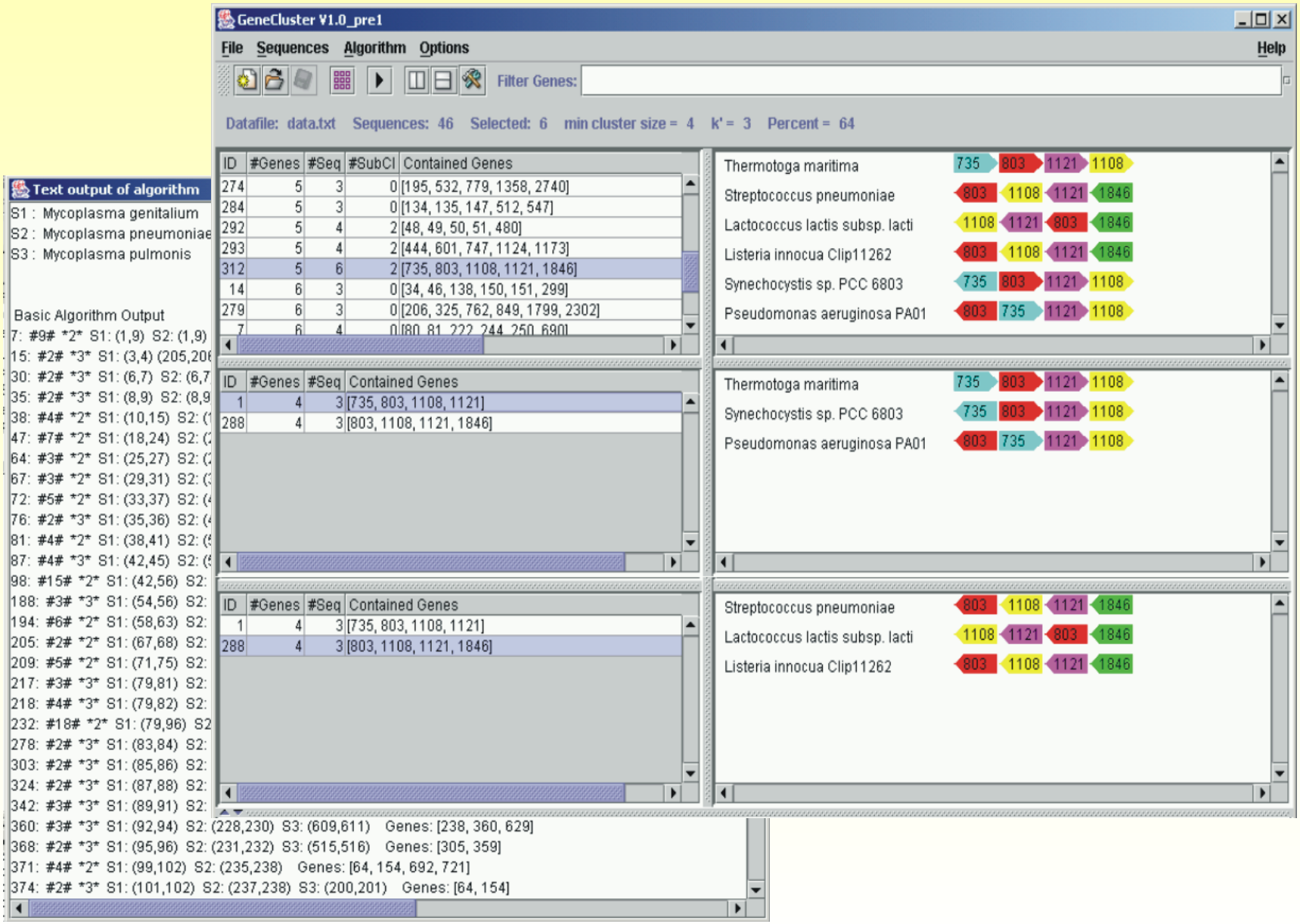
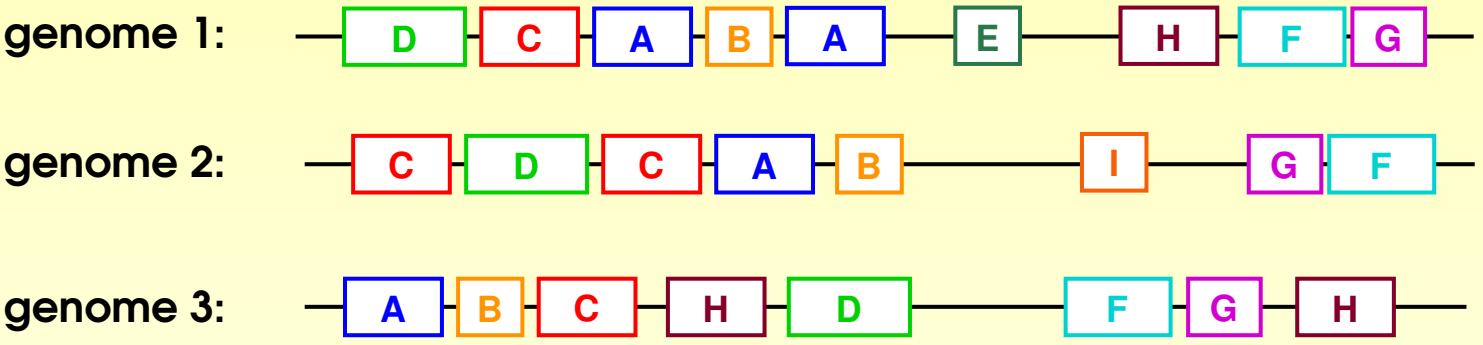


Approximate Gene Clusters



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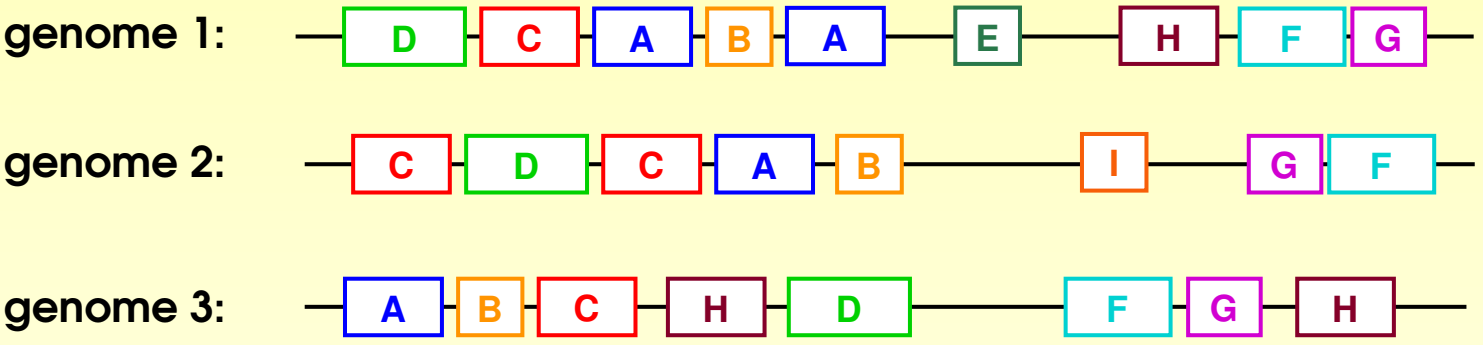
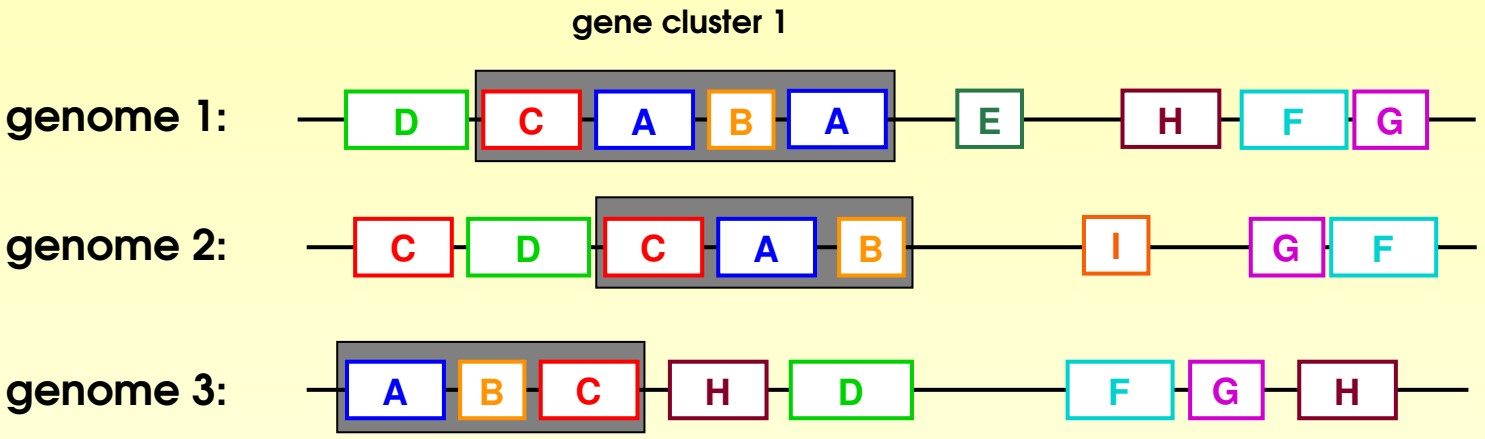


- (perfect) gene cluster:
  - set of genes occurring *en bloc* in multiple genomes
  - gene order within blocks not considered
  - multiple occurrences of genes possible

Approximate Gene Clusters



- (perfect) gene cluster:
  - set of genes occurring *en bloc* in multiple genomes
  - gene order within blocks not considered
  - multiple occurrences of genes possible

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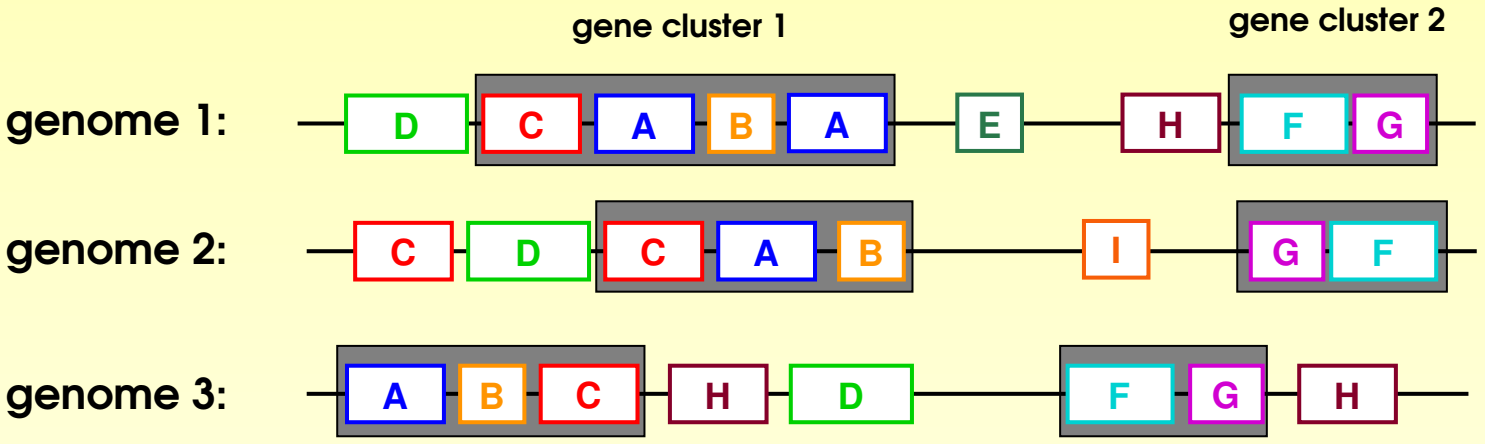

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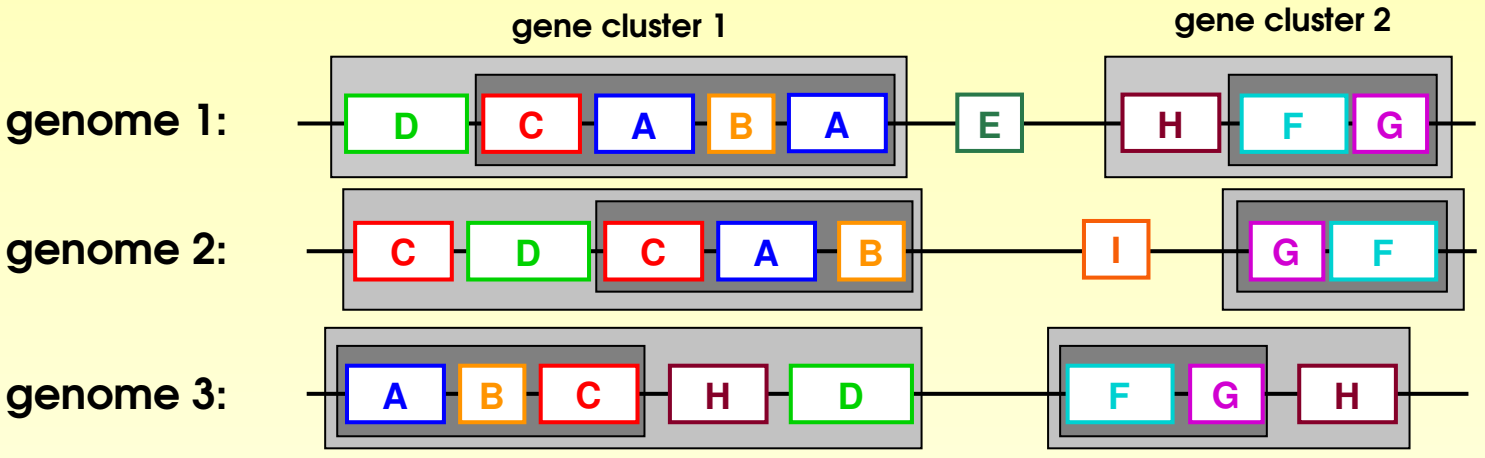

- (perfect) gene cluster:
  - set of genes occurring *en bloc* in multiple genomes
  - gene order within blocks not considered
  - multiple occurrences of genes possible
- approximate gene cluster:
  - additional and missing genes

Models for Approximate Gene Clusters

- *r*-window model (Friedman and Hughes, 2001)
  - fixed block size
  - pairwise comparison in polynomial time
- max-gap model (Bergeron, Corteel and Raffinot, 2002)
  - upper bound for insertion length
  - pairwise comparison in polynomial time
  - exponential in number of compared sequences
- approximate gene clusters (Rahmann and Klau, 2006)
  - very general cluster model, subsumes most other models
  - ILP approach
- **median gene clusters** (Böcker, Jahn, Mixtacki and JS, 2008)

Median of Character Sets

Sequence 1: . . . . . 1 2 3 4 5 6 7 . . . . . .
Sequence 2: . . . 1 8 3 4 5 2 1 6 7 9 . . . . . .
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Σ :	1	2	3	4	5	6	7	8	9
$CS(S_1(i_1, j_1))$	1	1	1	1	1	1	1	0	0
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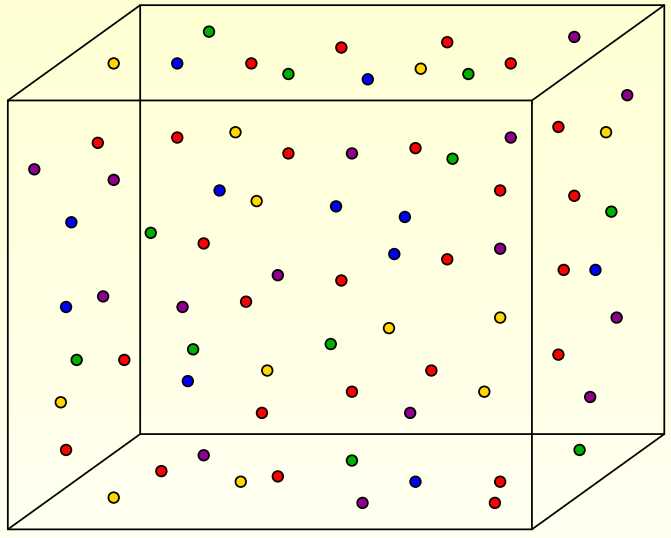
Space of Character Sets: $\{0, 1\}^{|\Sigma|}$



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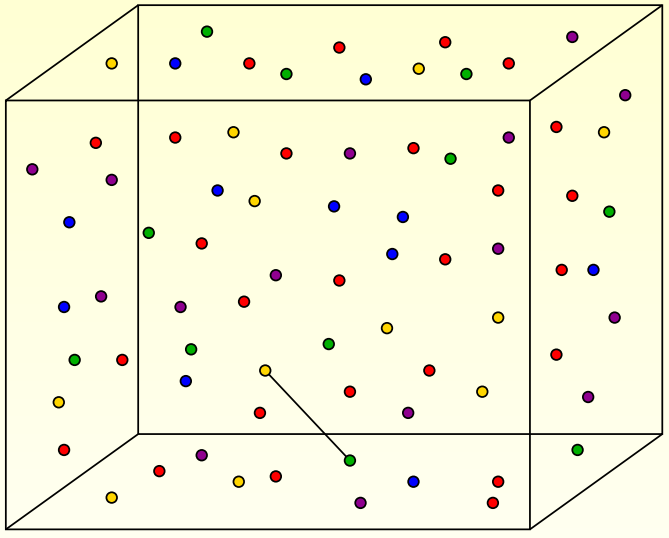

$$D_{sym}(C_1, C_2) = |C_1 \setminus C_2| + |C_2 \setminus C_1|$$

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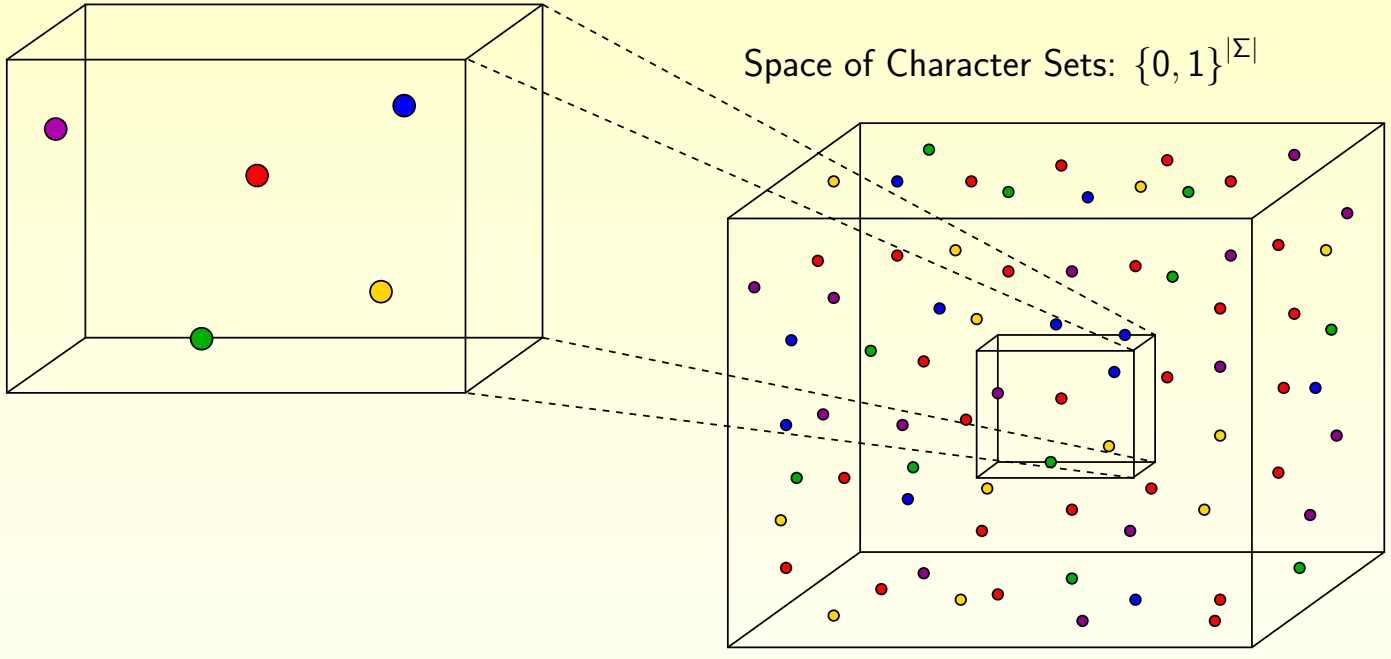

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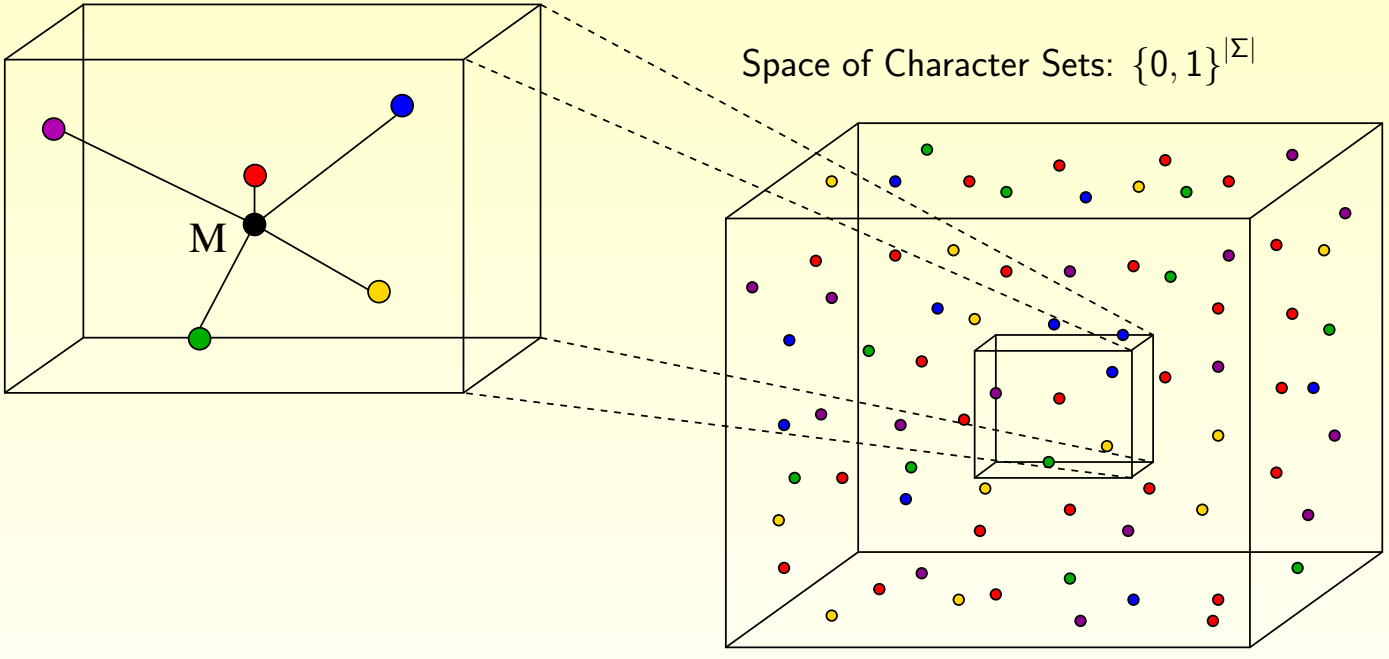

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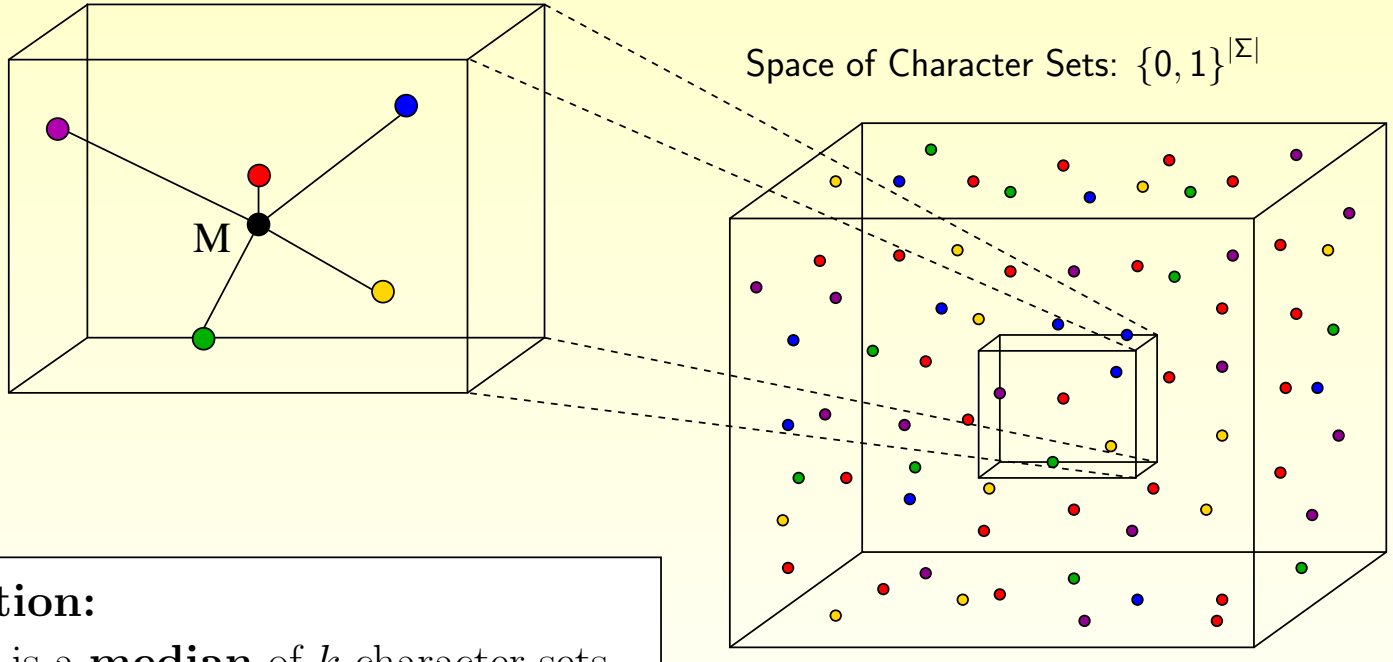


Definition:

$M \subseteq \Sigma$ is a **median** of k character sets $C_1, \ldots, C_k \subseteq \Sigma$ iff for all $C \subseteq \Sigma$:

$\Sigma_{\ell=1}^{k} D_{sym}(M, C_\ell) \leq \Sigma_{\ell=1}^{k} D_{sym}(C, C_\ell)$

$D_{sym}(C_1, C_2) = |C_1 \setminus C_2| + |C_2 \setminus C_1|$

Problem Statement

Given:

- sequences $S_1, \ldots, S_k$ over alphabet Σ
- s (minimum cluster size)
- δ (distance threshold)

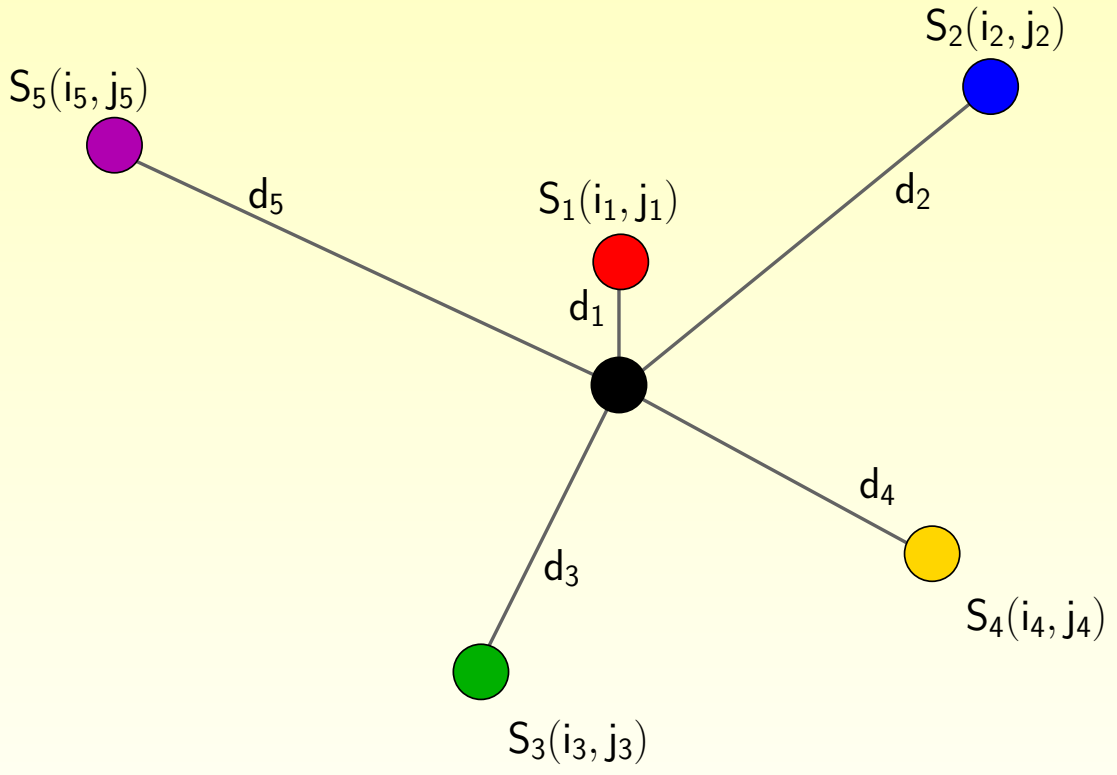
Wanted: all $M \subseteq \Sigma$ with

- M is a median for some $S_1[i_1, j_1], ..., S_k[i_k, j_k]$
- $\sum_{\ell=1}^{k} D\big(M, \mathcal{CS}(S[i_\ell, j_\ell])\big) \leq \delta$
- $|M| \geq s$

Such a set M is called a median gene cluster of $S_1, \ldots, S_k$.

Main Idea: Search Space Reduction

- search space: all $\mathcal{O}(n^{2k})$ combinations of substrings of $S_1, ..., S_k$
- cluster filter approach:



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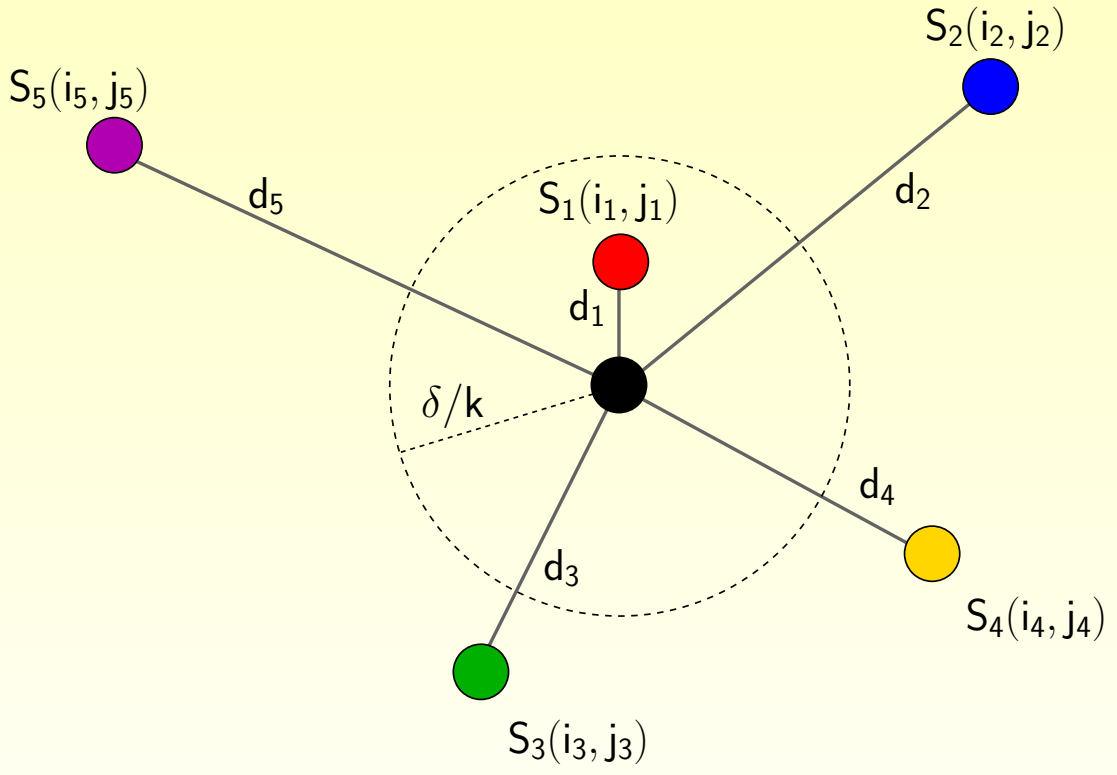

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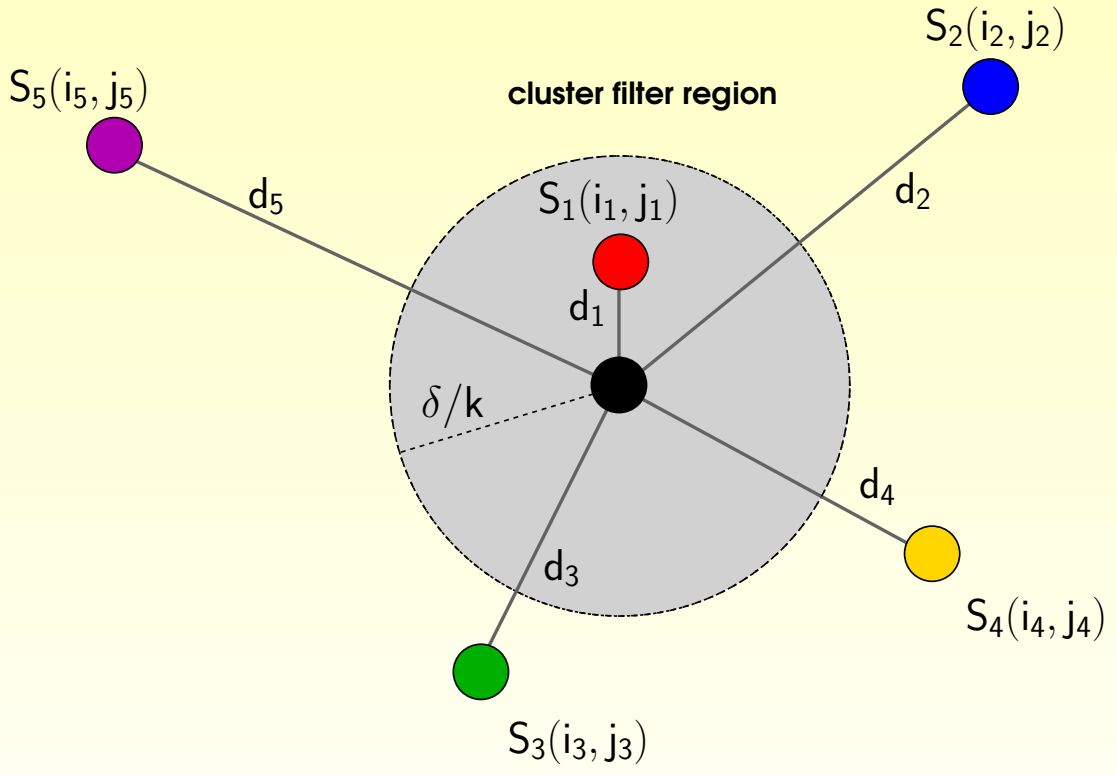

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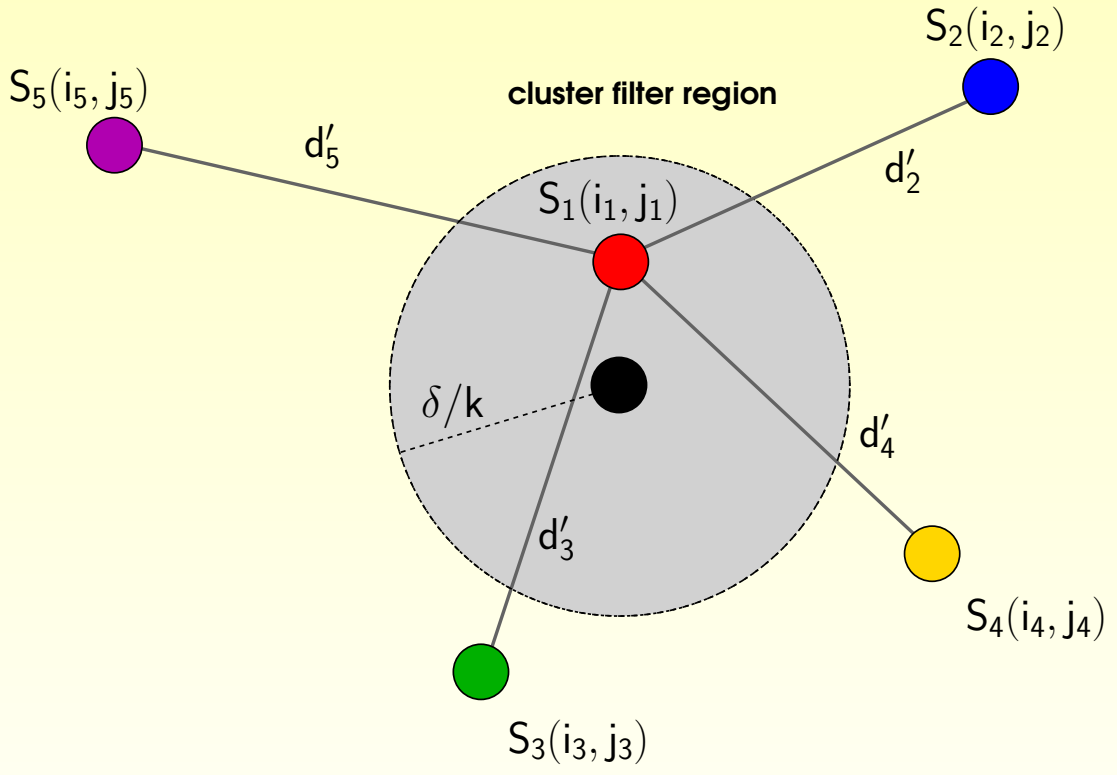


- median distance threshold: $\sum_{\ell=1}^{k} d_\ell \leq \delta$
- cluster filter distance threshold: $\sum_{\ell=1}^{k} d'_\ell \leq 2\frac{k-1}{k}\delta$

3-Step Approach to Median Gene Cluster Computation

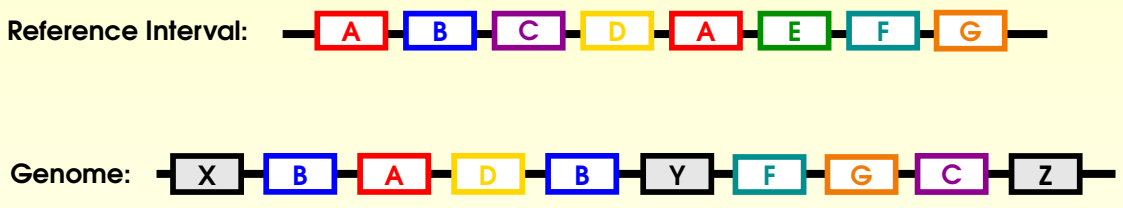
- Step 1: compute the set of all cluster filters C for $S_1, \ldots, S_k$
- Step 2: compute for each cluster filter C all combinations with substrings from the other sequences for which:

$$\sum_{\ell=1}^{k} D\big(C, \mathcal{CS}(S_\ell[i_\ell, j_\ell])\big) \;\leq\; 2\frac{k-1}{k}\delta$$

- Step 3:
  - computation of median(s) of each k-tuple (from Step 2)
  - comparison of median distance with distance threshold

Step 1: Computation of Cluster Filters

- naive approach: testing all $\mathcal{O}(k^2 n^4)$ combinations of substrings
- our approach: extension of the *Connecting Intervals Algorithm* (Schmidt and JS, 2004)



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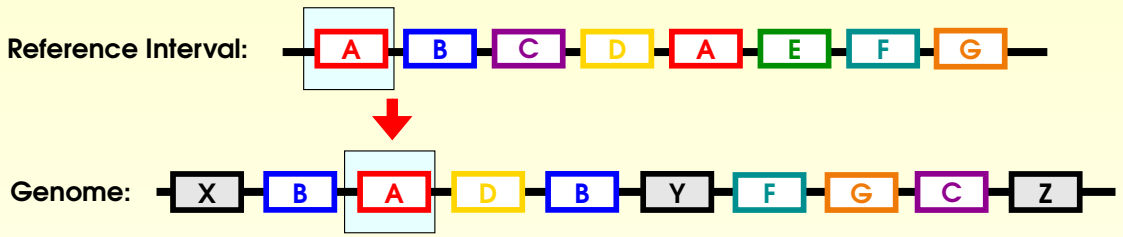

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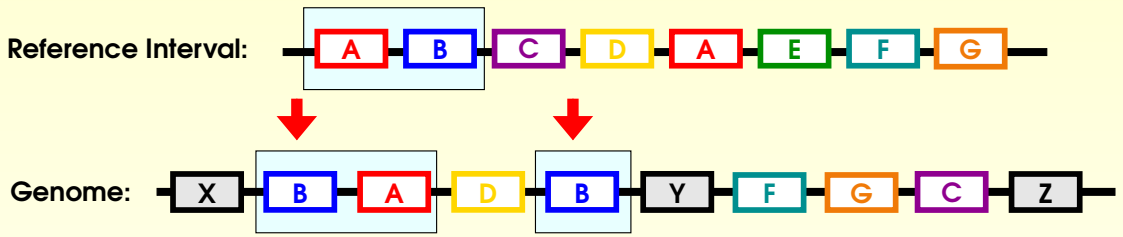

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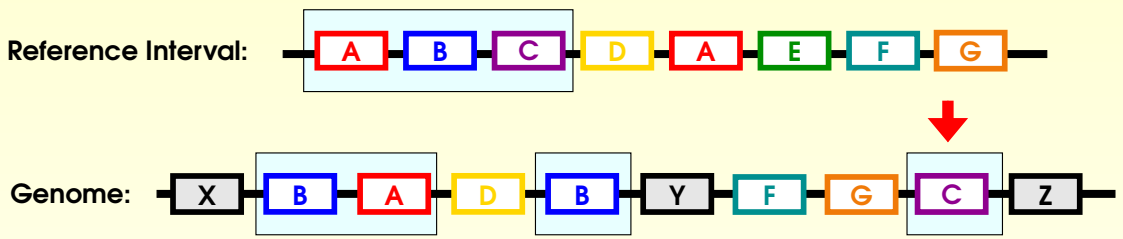

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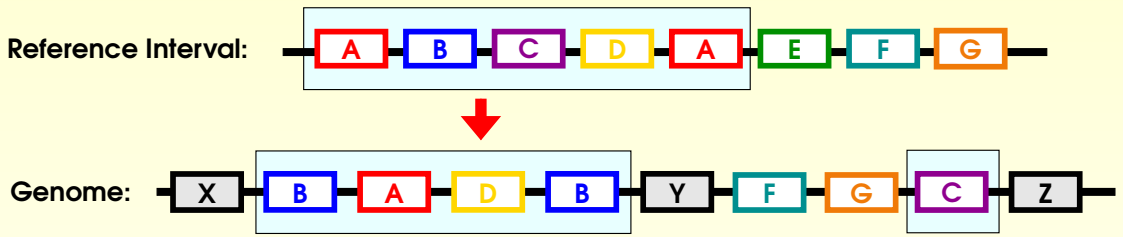

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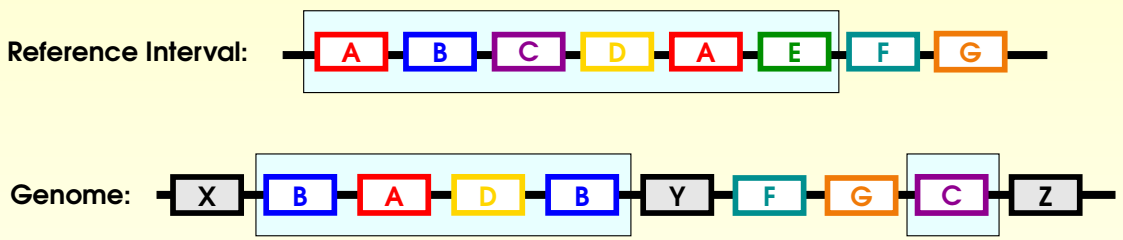

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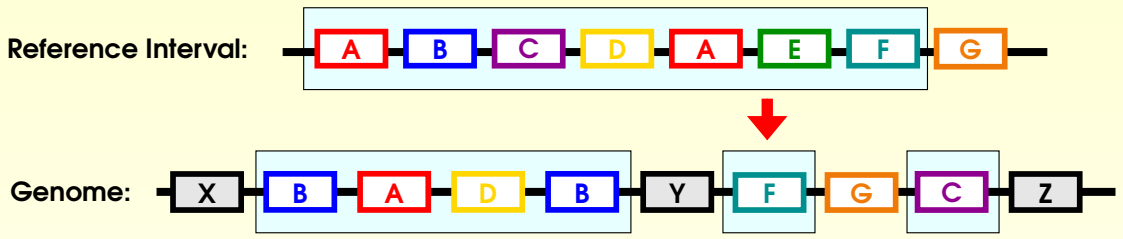

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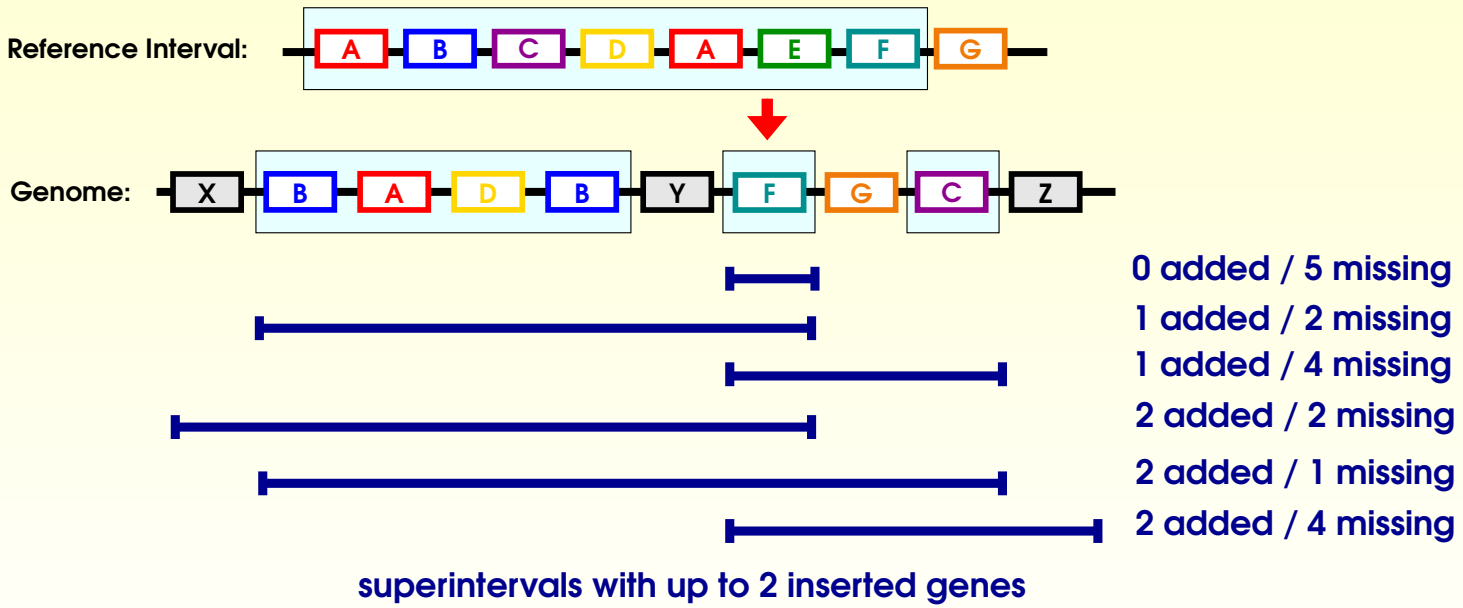

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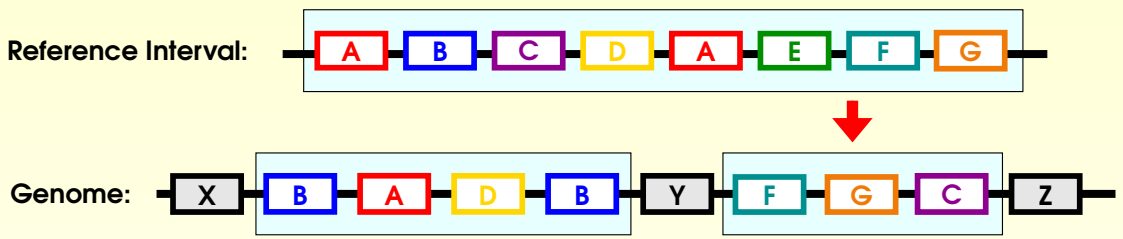

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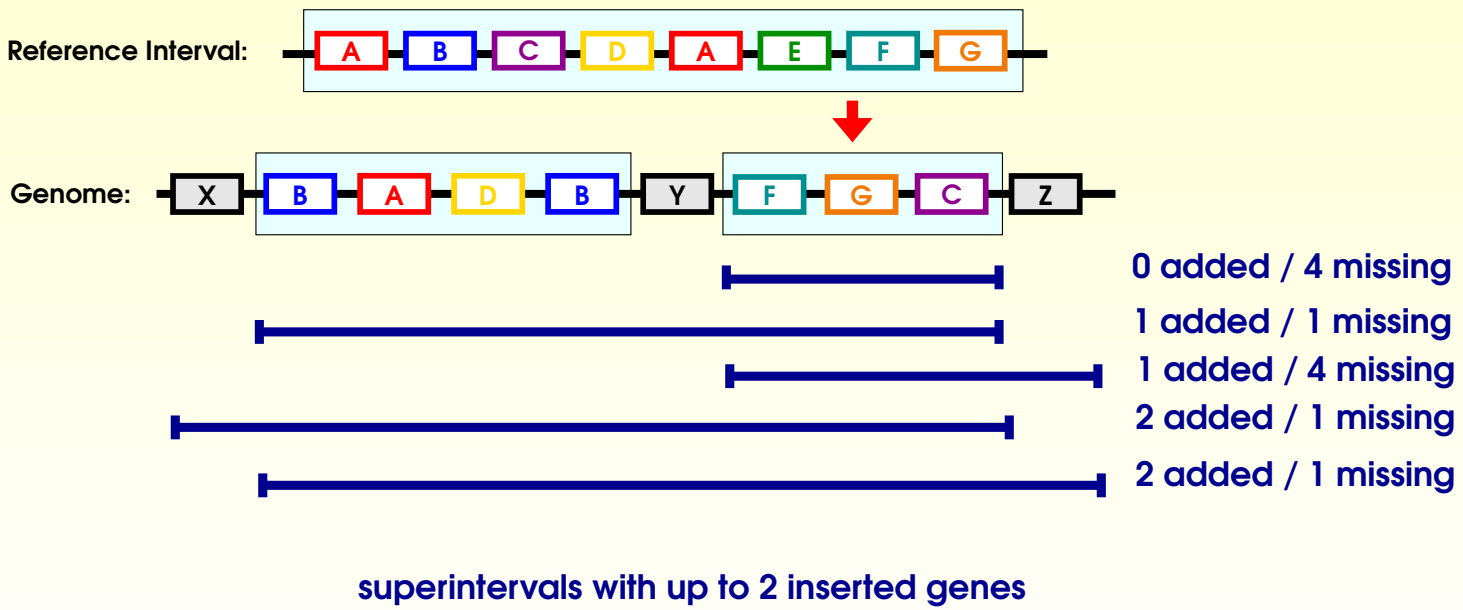

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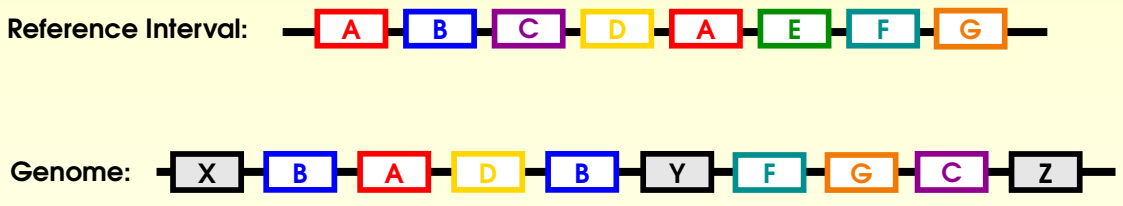
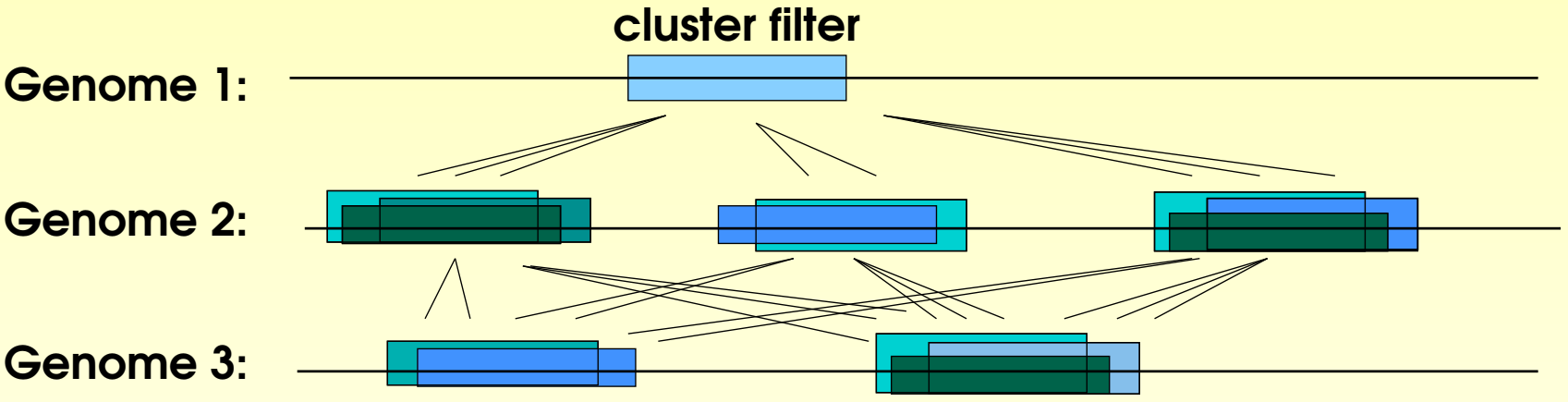


- runtime: $\mathcal{O}(k^2 n^2(1+\delta^2))$, space: $\mathcal{O}(kn^2)$

Step 2: Computation of k-Tuples Containing a Cluster Filter



Idea: Build for each cluster filter C all combinations with substrings of the other sequences for which C is cluster filter

- possible combinatorial explosion $\mathcal{O}(n^k)$ (unlikely in practice)
- up to $\mathcal{O}(\delta^{2k})$ variants of a k-tuple

Step 3: Computation of Median of Each k-Tuple

- majority vote: $\mathcal{O}(k|\Sigma|)$ time and $\mathcal{O}(k|\Sigma|)$ space
- compare total distance with threshold δ

	A	B	C	D	E	F	G	H	I	J
Genome 1	1	1	1	1	0	1	0	1	1	0
Genome 2	1	1	0	1	0	1	1	1	1	1
Genome 3	1	1	1	1	1	1	0	1	0	1
Genome 4	1	1	1	1	1	1	1	1	1	0
Genome 5	1	0	1	1	0	1	0	1	1	1
	5	4	4	5	2	5	2	5	4	3

Median = { A B C D F H I J }

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Algorithm Summary

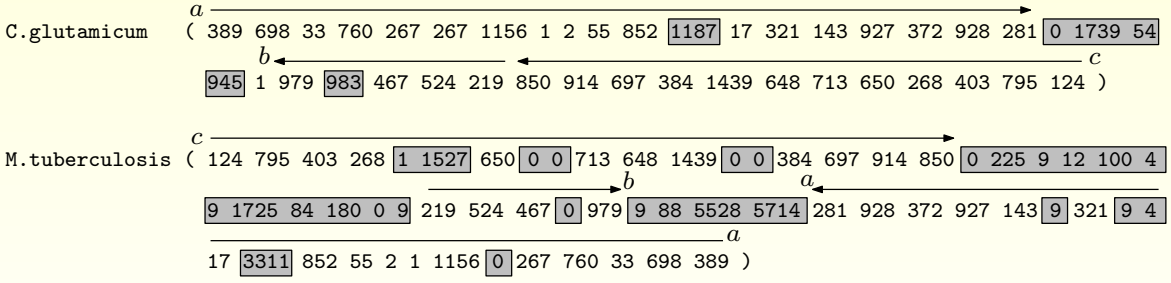
- Step 1: cluster filter computation $\mathcal{O}(k^2 n^2 (1 + \delta^2))$
- Step 2: combination of each cluster filter C with substrings from other sequences with

$$\sum_{\ell=1}^{k} D(C, \mathcal{CS}(S_\ell[i_\ell, j_\ell])) \leq 2\frac{k-1}{k}\delta$$

  possible combinatorial explosion: $\mathcal{O}(n^k)$
- Step 3:
  - computation of median of each such k-tuple $\mathcal{O}(k|\Sigma|)$
  - comparison: median distance vs. distance threshold δ

Experimental Results

- comparison with ILP approach (Rahmann and Klau 2006)
- dataset: genomes of *C. glutamicum* and *M. tuberculosis*
- detection of gene cluster containing 51 genes
- runtime of ILP program: $>$ 1h
- runtime of our approach: 17 sec. (on slower processor)



Experimental Results

- application to gene cluster detection in multiple genomes
- five γ-proteobacteria:
  - *Buchnera aphidicola APS (NC_002528)*
  - *Escherichia coli K12 (NC_000913)*
  - *Haemophilus influenzae Rd (NC_000907)*
  - *Pasteurella multocida Pm70 (NC_002663)*
  - *Xylella fastidiosa 9a5c (NC_002488)*

	δ=0	δ=1	δ=5	δ=8	δ=12
s=10	6	124	252	329	406
s=15	0	42	127	165	181
s=25	0	0	10	10	10

\# median gene clusters

	δ=0	δ=1	δ=5	δ=8	δ=12
s=10	6.9	7.4	20.0	103.4	1610.0
s=15	6.9	7.3	15.1	59.7	1148.5
s=25	6.9	7.1	10.5	17.6	630.0

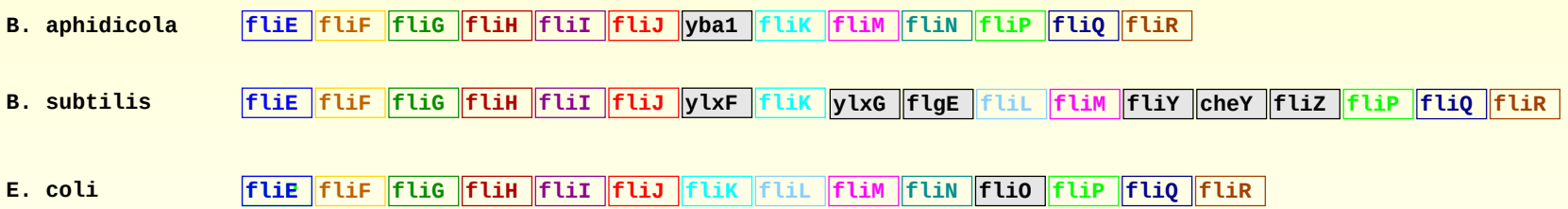
computation time (seconds)

Experimental Results

Sample gene clusters detected by our method:

- ATP synthesis

- flagellar biosynthesis



- cell division and cell wall biosynthesis

Algorithmic results

- Find all *common intervals* of k permutations in $\mathcal{O}(kn + |\text{output}|)$ time.
- Find all *common intervals* of k sequences in $\mathcal{O}(kn^2)$ time.
- Find all *median gene clusters* of k sequences in $\mathcal{O}(k^2n^2(1+\delta^2) + n^k + k|\Sigma|)$ time

Conclusion

Points raised:

- Comparative genomics can help in functional genome annotation
- Conserved regions in genomes have a static and a dynamic aspect
- Interesting combinatorics in Bioinformatics

Next steps:

- Statistical assessment of gene clusters
- Patterns in overlapping gene clusters
- Application to more data

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The end.