Gene Team Tree
A Compact Representation of All Gene Teams

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Outline

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Genome Evolution

- Genomes evolve via local and global changes
- Local changes act at the nucleotide level
- Global changes affects the *gene order*

Rearrangement type	**Effect on gene order**		
Reversal	a b c d e	$\Rightarrow$	a b e d c
Transposition	a b c d e	$\Rightarrow$	a c d e b
Inverted transposition	a b c d e	$\Rightarrow$	a e d c b
Insertion	a b _ c d e	$\Rightarrow$	a b f c d e
Duplication	a b _ c d e	$\Rightarrow$	a b a c d e
Deletion	a b c d e	$\Rightarrow$	a b d e

Table: Effect of rearrangements

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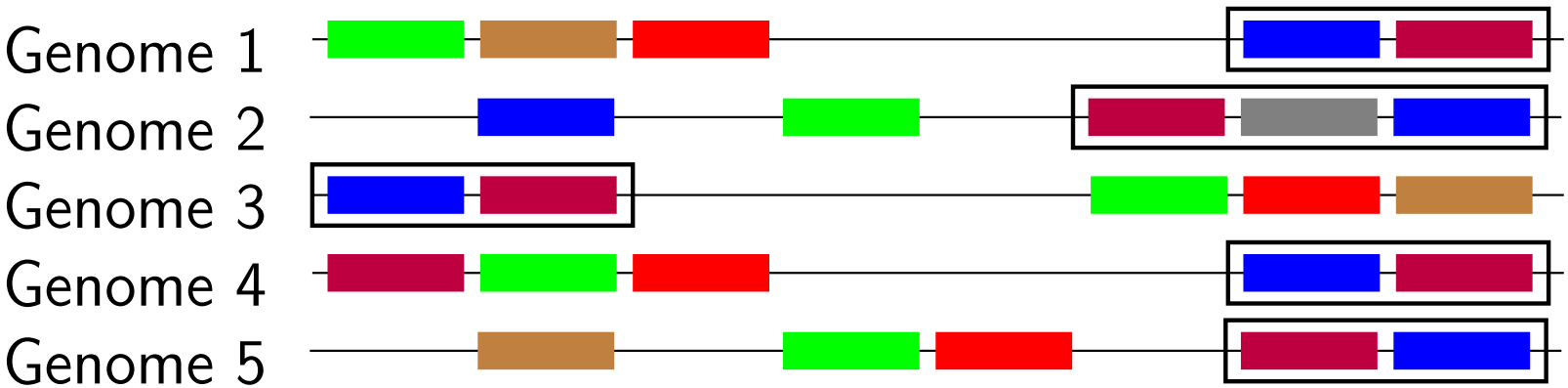

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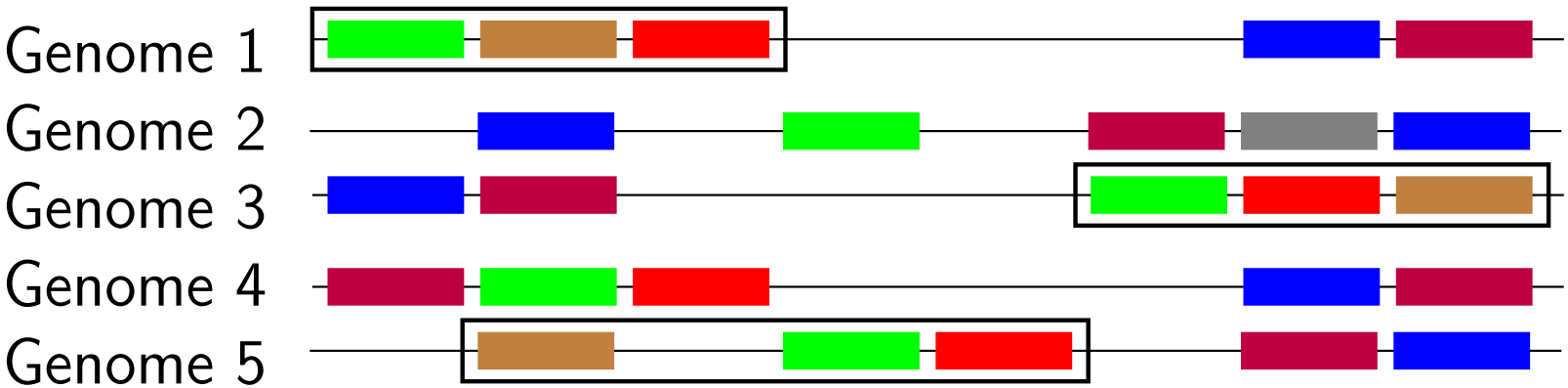

Applications

- Identify functional dependency/gene modules
- Identify large scale duplications/horizontal gene transfer

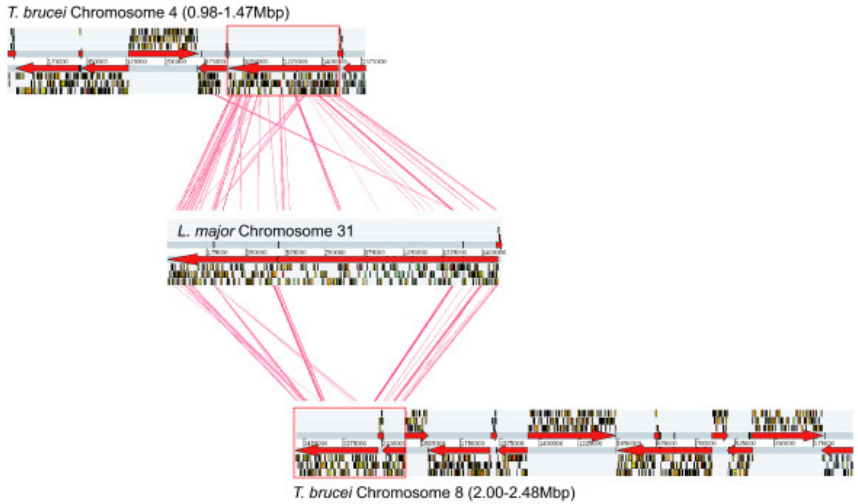

Figure: Trypanosoma brucei chromosomes 4 and 8 are partial duplicons [1]

- Measure of evolutionary distance

[1] Jackson, BMC Genomics 2007

Gene Teams: A model for conserved gene clusters

Gene Team

A maximal set of genes such that the distance between consecutive genes in all gene orders is at most δ [a].

[a] He and Goldwasser, JCB 2005

Example

$\delta = 2$

G : a b * * * a * c b

H : c * * c b a * b

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FindTeams algorithms for Gene Teams

Observation

A gene order can be divided across gaps which are longer than δ [a].

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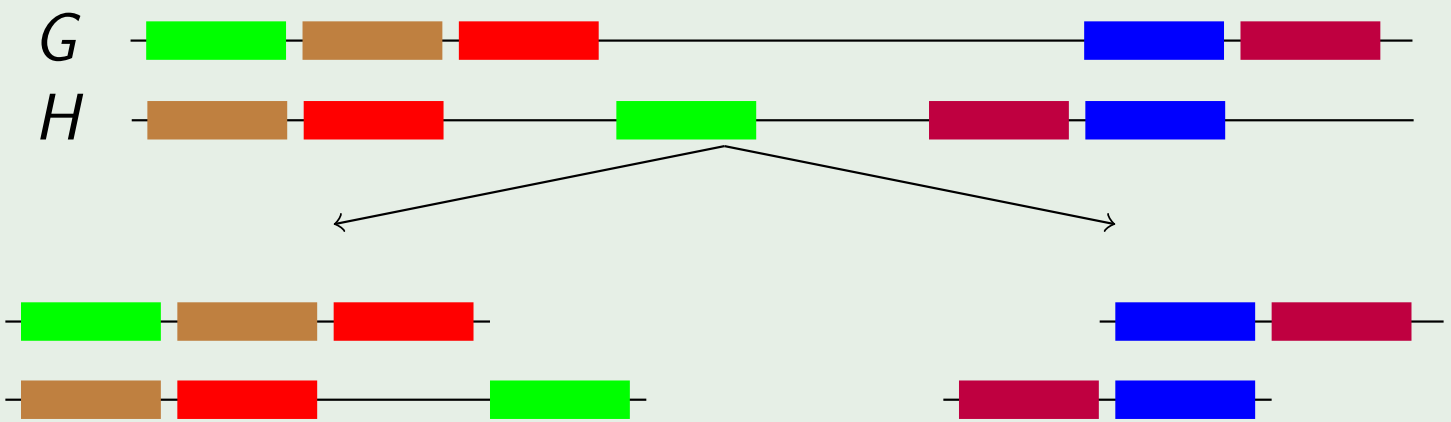

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Gene Teams in Practice

Problem: How to determine the "right" value of δ ?

δ is affected by:

- arrangement and distance between the genes
- rate of rearrangements
- type of conserved gene cluster, e.g. pathways, operons, etc.

Existing Approach

Benchmark against known conserved structures

1. Select a small number of known operons
2. Pick minimum δ so that selected operons were reconstructed. [a]

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Drawbacks

- May not have prior knowledge of conserved structures.
- How to select a representative set of known operons?

Our Approach

Key idea

- Find gene teams for ALL values of δ (this paper).
- Apply application specific tests to determine significance (ongoing work).

Key Observations

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Decreasing δ causes existing teams to split into smaller teams.

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Implication

Set of all gene teams can be compactly represented as a tree.

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Implication

We can do better than brute force.

Our Gene Team Tree

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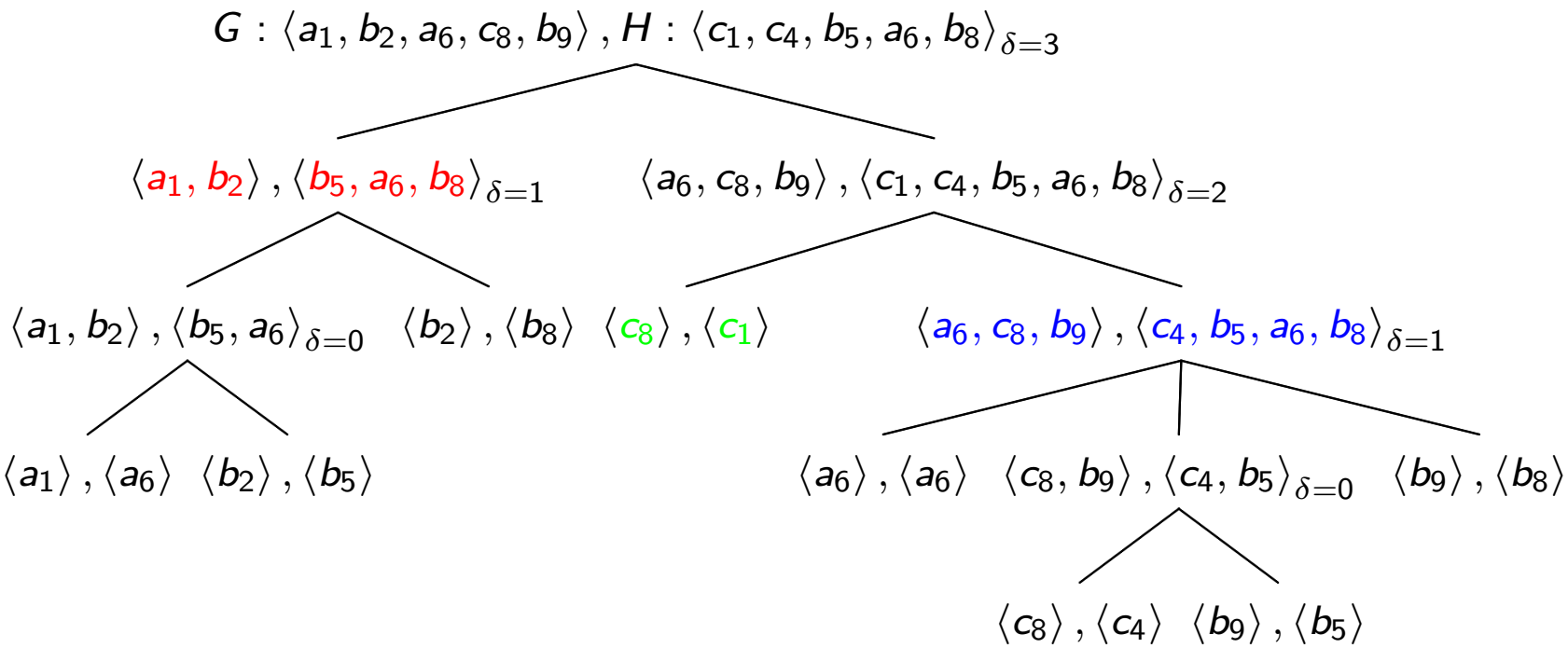

Figure: Gene team tree of G and H, value of δ used to split each node is show in subscripts. Colored nodes represent the gene teams for $\delta = 2$.

Our Main Results

Gene Team Tree Model

A compact representation of ALL gene teams.

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Algorithms to compute the GTT

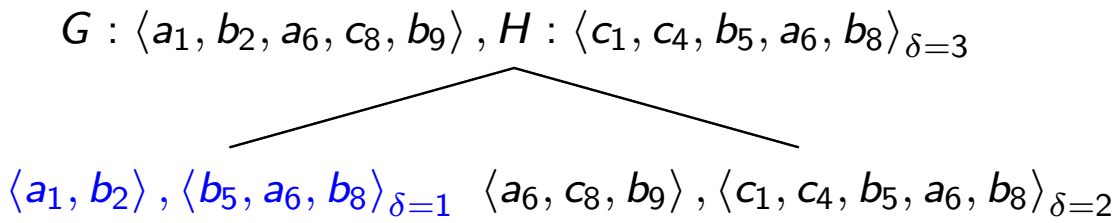
Generalize existing gene team mining algorithms with the *same worst case time complexity*.
$O(mn \lg^2 n)$ for m permutations of length n and
$O(\prod_{i=1}^{m} n_i)$ for m sequences of lengths $n_1, n_2, \ldots, n_m$.

Basic Algorithm

$$G : \langle a_1, b_2, a_6, c_8, b_9 \rangle, H : \langle c_1, c_4, b_5, a_6, b_8 \rangle_{\delta=3}$$

- Set $\delta = \textsc{MaxGap}(\text{team}) - 1$
- Run existing $\textsc{FindTeams}$ algorithms to determine children.

Basic Algorithm



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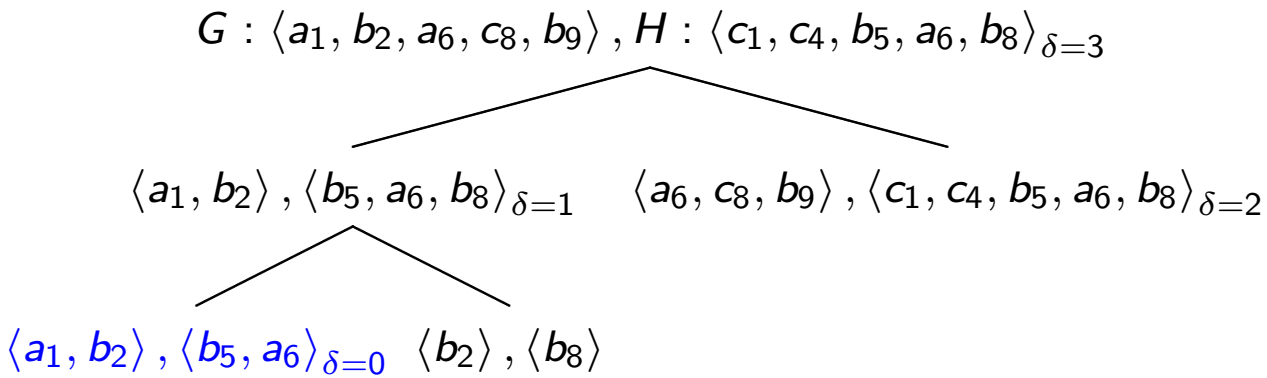

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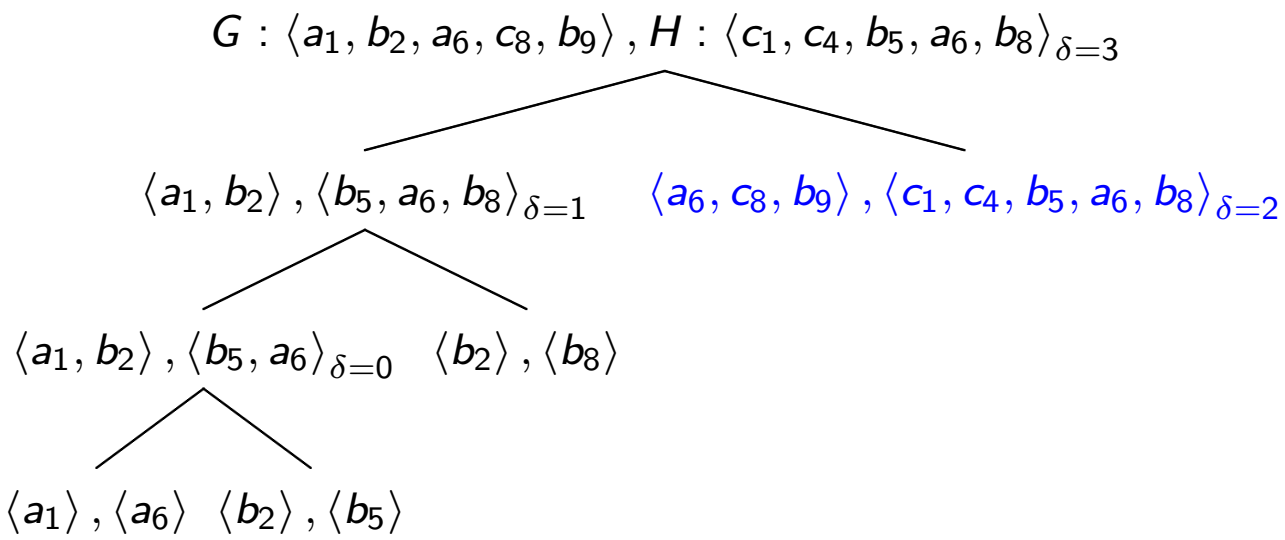

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Speeding Up GTT Computation

Key insight

Instead of treating FindTeams as a black box, integrate computation of GTT into FindTeams.

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Details

- Modify base case of FindTeams reduce δ and continue.
- Implement MaxGap efficiently using heap.

Outline

Summary of Datasets

Prokaryote dataset (uni-chromosomal)

#homology families	1137 from He and Goldwasser, JCB 2005
#genes in *E. coli* K-12	2332
#genes in *B. subtilis*	2339
running time	4s [a]

[a] on a 2.33GHz processor

Eukaryote dataset (multi-chromosomal)

#homology families	12662 from Fu et al., RECOMB 2006
#genes in human	14193
#genes in mouse	14442
running time	5s [a]

[a] on a 2.33GHz processor

Gene Team Tree for *E. coli* K-12 and *B. subtilis*

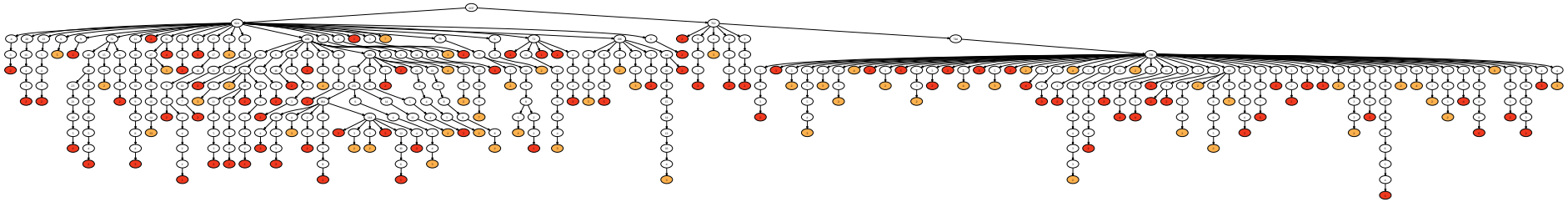

Figure: GTT for *E. coli* K-12(2332 genes) and *B. subtilis*(2339 genes) with 1137 homology families

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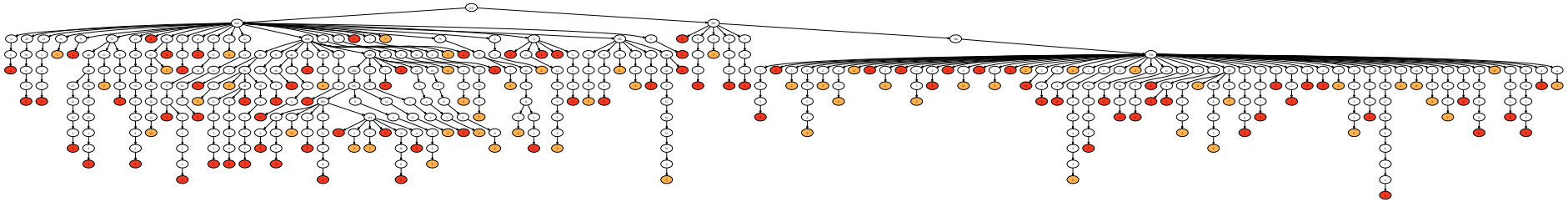

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Question

Does our GTT allows us to identify more operons as compared to using a single fixed value of δ?

Compare GTT against operons of *E. coli* K-12

1. Download set of *E. coli* K-12 operons from RegulonDB
2. For each operon, find best matching gene team in GTT based on Jaccard index

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Focus on 138 (out of 250) operons with Jaccard index $> 2/3$.
Recall: Gene team exists within a range of δ values, $[\delta_{\text{min}}, \delta_{\text{max}}]$

$$G : \langle a_1, b_2, a_6, c_8, b_9 \rangle, H : \langle c_1, c_4, b_5, a_6, b_8 \rangle_{\delta=3}$$

$$\langle a_1, b_2 \rangle, \langle b_5, a_6, b_8 \rangle_{\delta=1} \quad \langle a_6, c_8, b_9 \rangle, \langle c_1, c_4, b_5, a_6, b_8 \rangle_{\delta=2}$$

Range of δ for recovered operons

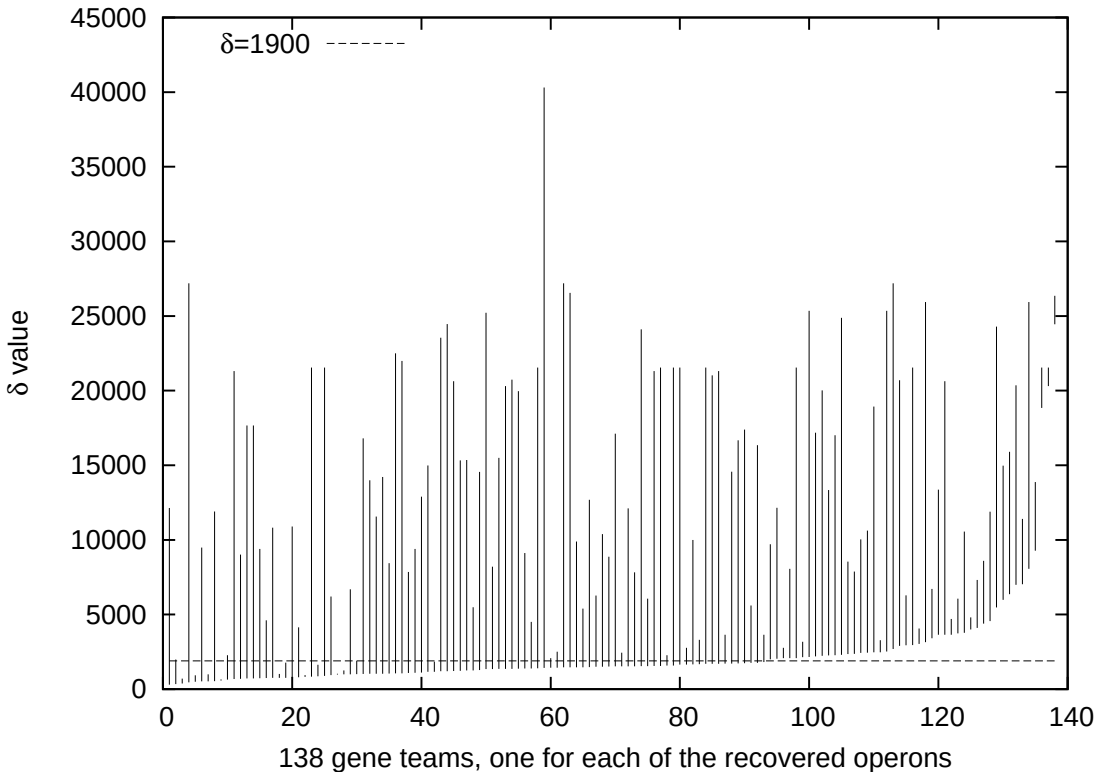

Figure: $[\delta_{\text{min}}, \delta_{\text{max}}]$ for best match gene teams, arranged in increasing δ_{min}

Wide variation in range of δ, more investigations are ongoing.

Number of recovered operons versus δ

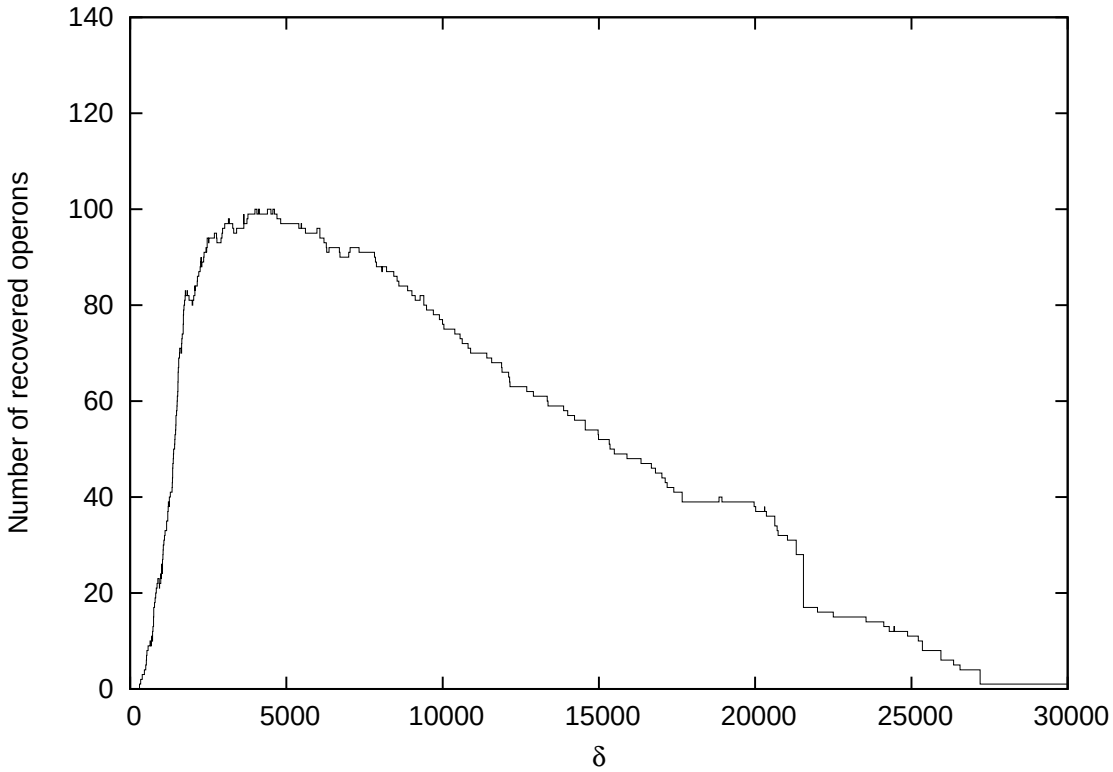

Figure: Number of recovered operons for different values of δ

$\delta = 1900$ recovers 81 operons. No single value of δ can obtain all the best matched gene teams.

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- GTT can be computed efficiently by modifying existing parametrized algorithms.
- Analysis of *E. coli* K-12 operons confirms that no single value of δ can produce all gene teams which is best match to known operons.

Future Work

- More datasets and compare against higher order mechanisms.
- Find segmental duplications via self comparison.
- Close the gap between performance of algorithms for permutations and sequences.

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For downloads and updates on this project, please visit
`http://wwww.comp.nus.edu.sg/~melvin/GTT`