

A Novel Approach for Comparative Genomics & Annotation Transfer

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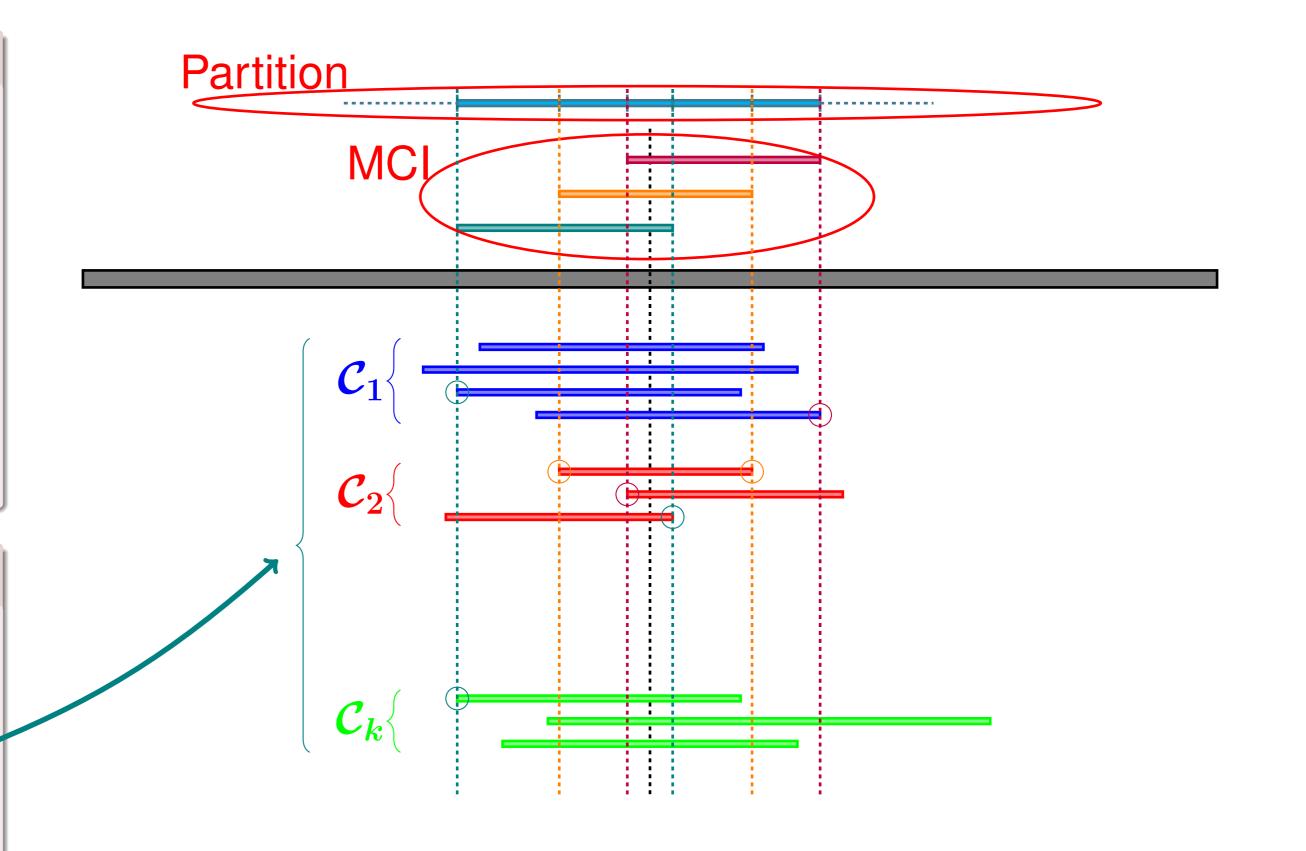


Context "What is genome comparison good for?"

Genome comparison

- is crucial for genome annotation, regulatory motifs identification, and vaccine design
- aims at finding genomic regions either specific to or in one-to-one correspondence between individuals/strains/species
- proves useful to transfer annotations from a known genome to a new one
- However, current methods do not suit the whole spectrum of applications and genome sizes.

Innovative approaches are still needed

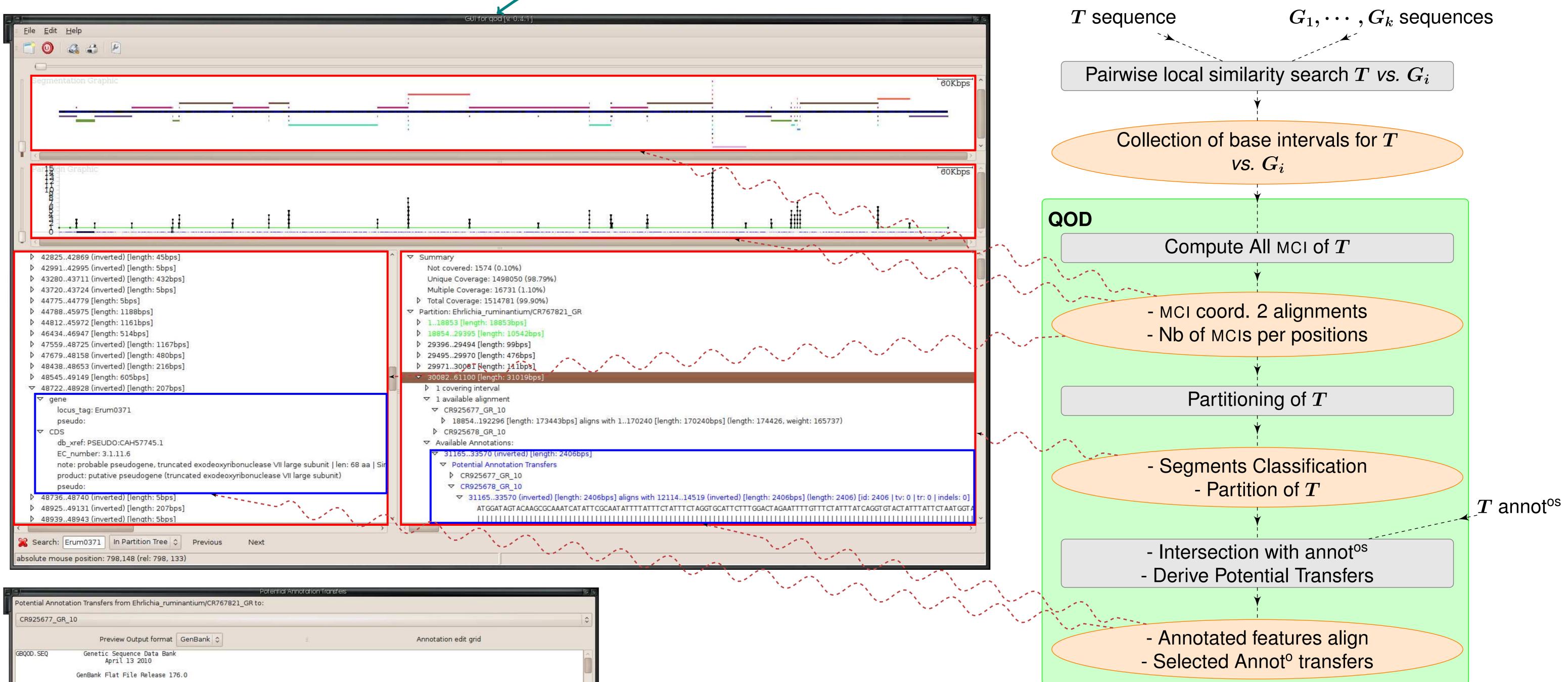


QQD: a novel approach to genome comparison

We propose, QQD, an approach to whole genome comparison that differs from multiple alignment:

- it compares one target genome to k reference genomes
- uses as input pairwise local alignments (BLAST-like) between the target and each of the references
- it computes on the target genome all Maximum Common Intervals (MCI, see Definition)
- MCI: maximal region from the target that can be aligned pairwise to regions in each of the references
- QQD partitions the target genome into regions that are
 - Inot alignable with each reference genome
 - 2 shared, but having a single alignment possibility in each reference genome
 - Shared with several potential alignments
- Class 2 regions have potential orthologs in the other genomes, Class 1 regions help finding genome specific regions.

The MCIS, the partitions, and annotations features are visualized and browsable on the GUI.

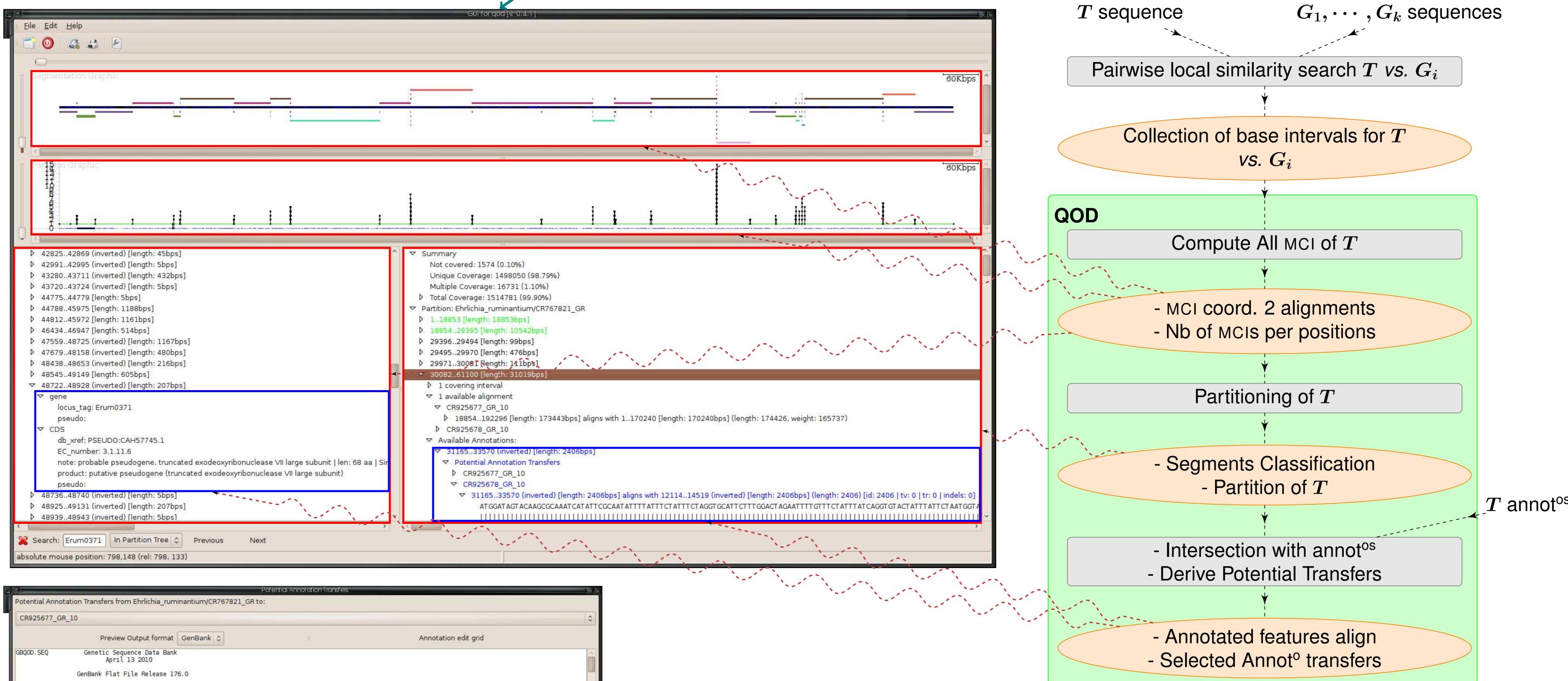


Maximal Common Intervals (MCI)

For $1 \leq i \leq k$, let C_i be the set of local alignments between target genome T and reference genome G_i .

An interval J is common to all $C_{1 \le j \le k}$ if and only if for any collection C_j there exists an interval say I_i^j from \mathcal{C}_j such that $J \subseteq I_i^j$.

Assume J = [p,q] with p < q is a common interval. J is said to be a *maximal* if neither [p-1,q] nor [p,q+1] are common intervals.



and Sequence god annotation 194 gene (95.1691%) complement(29613..29819) Start End Feature Qualifier Value /locus_tag="Erum0371 29819 29613 gene locus_tag Erum0371 pseudo god annotation 195 CDS (95.1691% complement(29613..29819) Start End Feature Qualifier db xref="PSEUDO:CAH57745.1 C number="3.1.11.6" 29819 29613 CDS ote="probable pseudogene, truncated exodeoxyribonuclease" PSEUDO:CAH57745.1 db xref large subunit | len: 68 aa | Similar to the N-terminus o several e.g. EX7L ECOLI Exodeoxyribonuclease VII large su EC_number 3.1.11.6 ounit (456 aa) from Escherichia coli, fasta scores: E(): 6e -05, 39.683% identity in 63 aa overlap | Almost identical t probable pseudogene, truncated exc note o Erum0372 and the N-terminus of Erum0370"

Annotation Transfer

QOD

intersects the target genome's annotations with regions from the partition, and derives for annotation in shared region their pairwise alignments

QQD declares as **potentially transferable**

e VII large subunit) pseudo /pseudo=" qod_annotation_200_gene (97.1599%) omplement(29834..30484) Start End Feature Qualifier Value /locus_tag="Erum0380" 30484 29834 gene locus_tag Erum0380 3 qod_annotation_201_CDS (97.1599%) complement(29834..30484) Start End Feature Qualifier /db xref="UniProtKB/TrEMBL:Q5HCD9 'note="probable membrane protein | len: 222 aa | Almost ide 30484 29834 CDS tical to Q93FQ3 Hypothetical 6.6 kDa protein (Fragment) (58 a) from Ehrlichia ruminantium (Gardel), fasta scores: E(] db xref UniProtKB/TrEMBL:05HCD 7.1e-16, 96.552% identity in 58 aa overlap | Contains 1 note probable membrane protein | len: 222 bable transmembrane helix predicted by TMHMM2.0 at aa 88 105 | C-terminus ends within a tandem repeat, 203 bp repeat product nutative membrane prote Number of annotations to display < << < >>>> Go to page Filters Select potential transfer having %id at least 95 Enabled features Enabled qualifier exon 🖌 allele gap anticodon GC_signal 👿 bio material 🛃 gene bound_moiety Select All Features Select All Qualifiers Unselect All Features Unselect All Qualifiers Save 🕲 <u>H</u>elp 🚽 Quit

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all features falling entirely in a region offering only one alignment possibility the user can interactively select among those features to transfer according to various criteria: alignment's percent of identity, feature class, etc.

QOD features

- is fast, flexible, interactive
- works on multiple OS
- exploits multi-core computers

accepts gzip compressed inputs

- can process unassembled/unfinished genomes
- distributed under CÉCILL license (GPL compliant).

Conclusion

• QQD is a different and novel approach to compare multiple whole genomes

Case study on bacterial strains of E. ruminantium exhibits 92 genes and many orthology relationships that have been missed by previous genome sequencing and comparative projets.

More informations are available at http://www.atgc-montpellier.fr/qod/

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Abstract

With the rapid development of sequencing techniques, the situation where a newly sequenced genome needs to be annotated using available genomes from close species should become more prevalent in the future. However, because of the cost of genome finishing we may have to handle incomplete or not fully assembled genomes. Undoubtedly, the need for comparative annotation will increase, but the genomic community still lack computational solutions that are both efficient and sensitive under various conditions. Present approaches are mainly based on the sequence similarity detected at the gene or protein levels, which are mostly further analysed independently one of each other, despite the dependency implied by the genome.

Hence, we propose a novel approach to genome comparison and use it to develop a system that transfers annotations between the compared genomes. Besides features' sequence similarity, it accounts for the synteny it detects across multiple genomes. This approach is simple for it avoids to solve complex questions that makes other approaches computationally hard.

The underlying idea is to partition a focus genome according to its pairwise similarities with the other compared genomes. The question is formulated as searching for the intervals that are shared across all genomes under consideration, and maximal in length (*i.e.*, not extendible). If a genomic region is covered by at least one interval it is conserved across all genomes, and the number of such intervals tells how many possibilities exist for aligning it with different regions of the other genomes. Hence, our algorithm partitions the genome into regions following two criteria: 1/ being shared or unshared across all genomes, 2/ offering a unique or several alignment possibilities. The annotation transfer procedure crosses the focus genome's annotations with these regions and automatically derives the possible alignments for each feature. All features falling entirely in a region offering only one alignment possibility are declared as *potentially transferable*, and the user may interactively select among those according to various criteria: alignment's percent of identity, feature class, etc.

We implemented these procedures in an efficient and flexible tool, named QQD, equipped with a user-friendly graphical interface. Graphical and textual results representations allow both to grasp the overall genome similarity at a glance and to browse the conserved and unshared features in various ways. This enables the investigation of genome specific genes or of rearrangements, and copy number variations, for instance. For it does not require the genome sequence to be completely assembled, our approach allows to compare and pre-annotate unfinished genomes, as well as assemblies of Next Generation Sequencing data.

Keywords: *bioinformatics, comparative genomics, computational tools, evolution, genomic structure*

Web Page: http://www.atgc-montpellier.fr/qod/