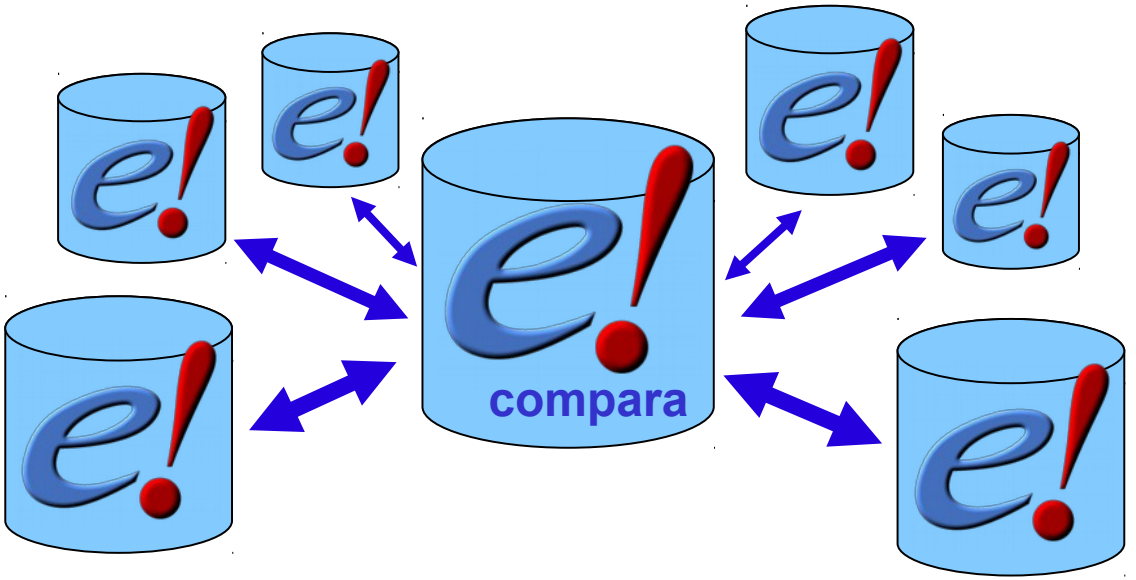
Ensembl Compara Perl API



Carla Cummins & Matthieu Muffato

API workshop - EBI

Sept 2015

Outline of the course

- Introduction about Compara
  - Resources
  - API
- Inputs
  - Species, Chromosomes, Genes
- Outputs
  - Gene analyses
  - Genome analyses

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What is Ensembl Compara?

A single database which contains precalculated comparative genomics data and which is linked to all the Ensembl Species (69 in e81) databases.

Access via perl API and mysql

A production system for generating that database

(not in this presentation)

The genomes in Ensembl

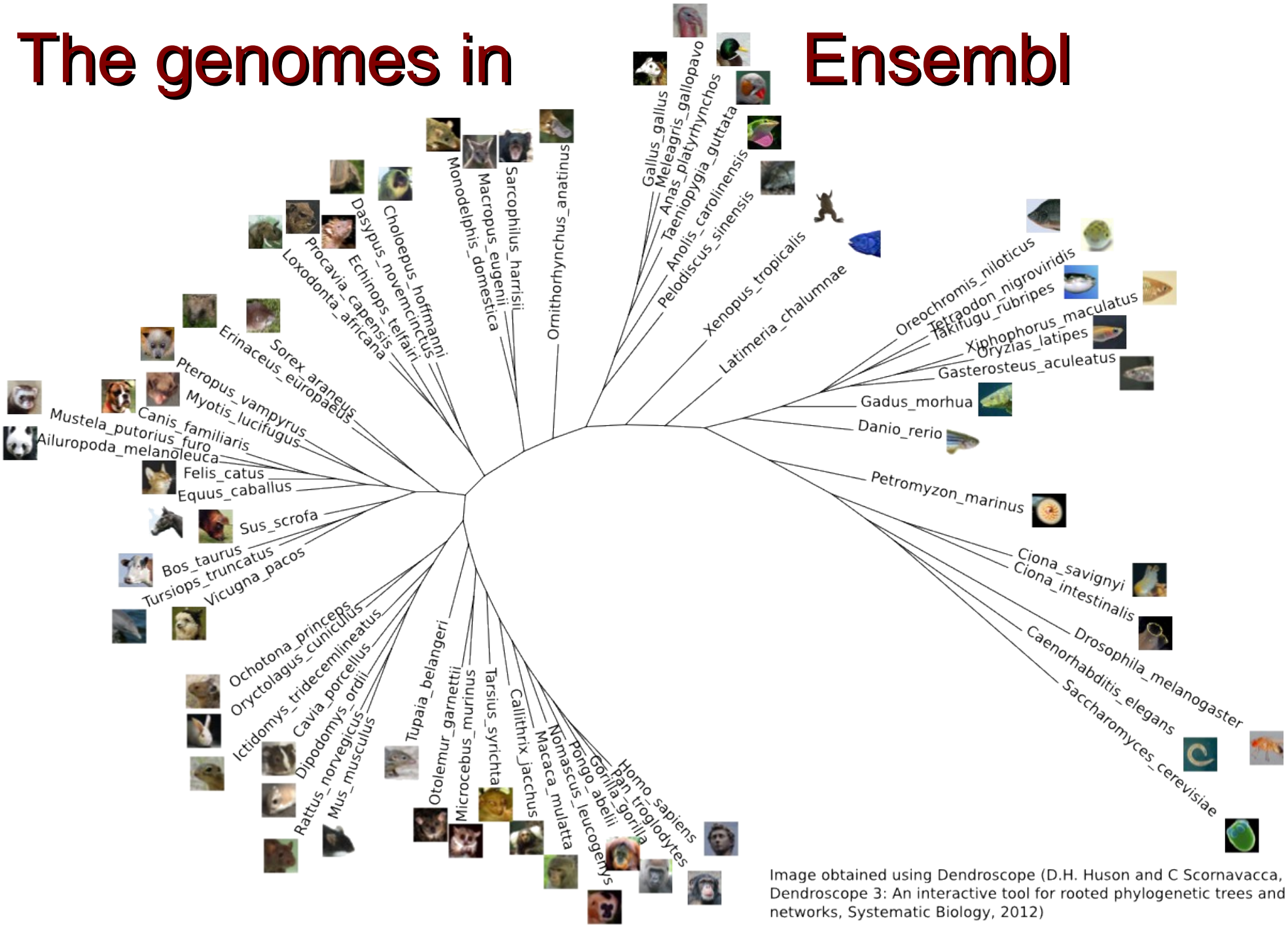


Image obtained using Dendroscope (D.H. Huson and C Scornavacca, Dendroscope 3: An interactive tool for rooted phylogenetic trees and networks, Systematic Biology, 2012)

Compara data

Genome level

Whole genome alignments (pairwise and multiple)

Constrained elements (based on multiple align.)

Syntenic regions (based on pair-wise align.)

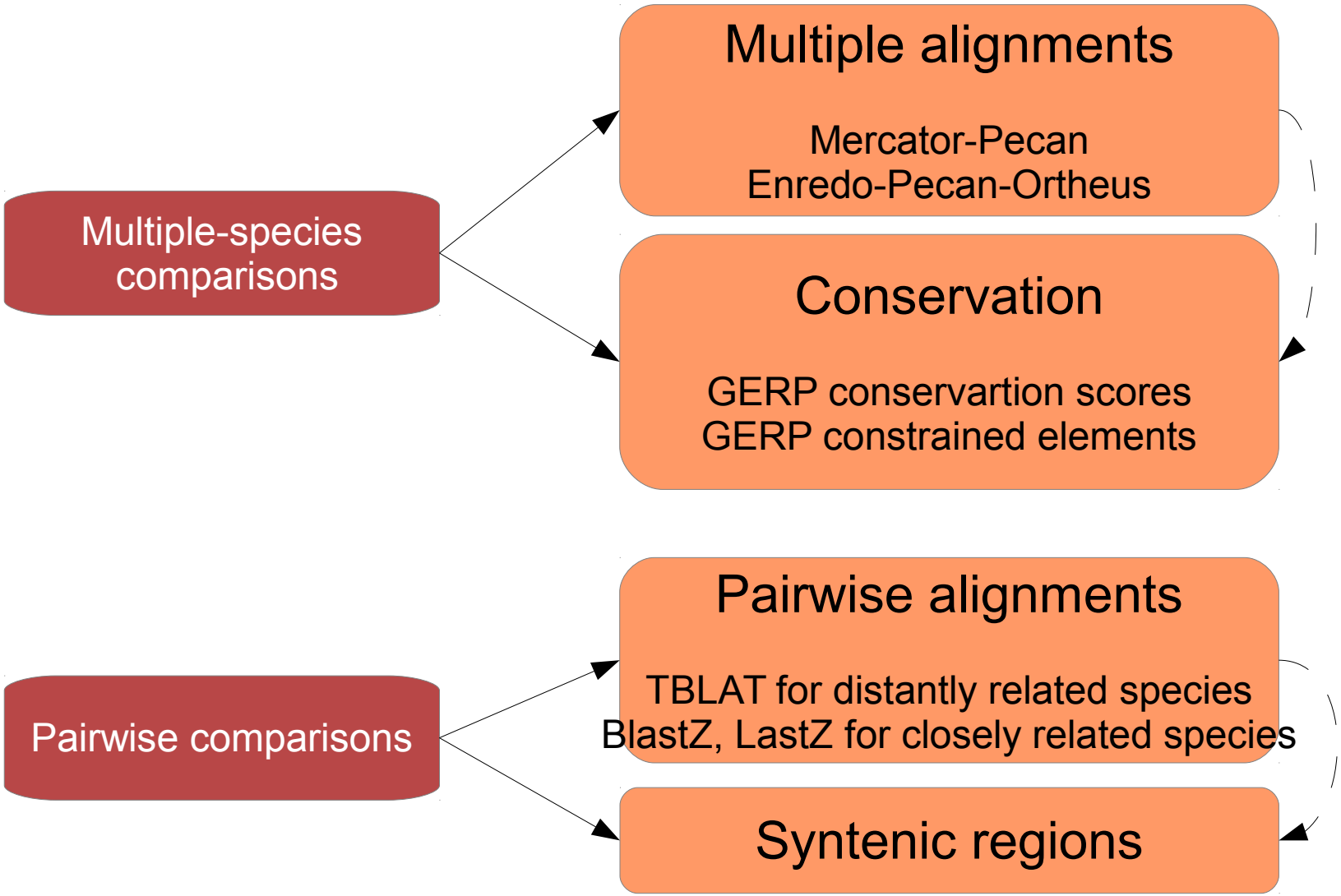
Gene level

Families (clusters of proteins + multiple align.)

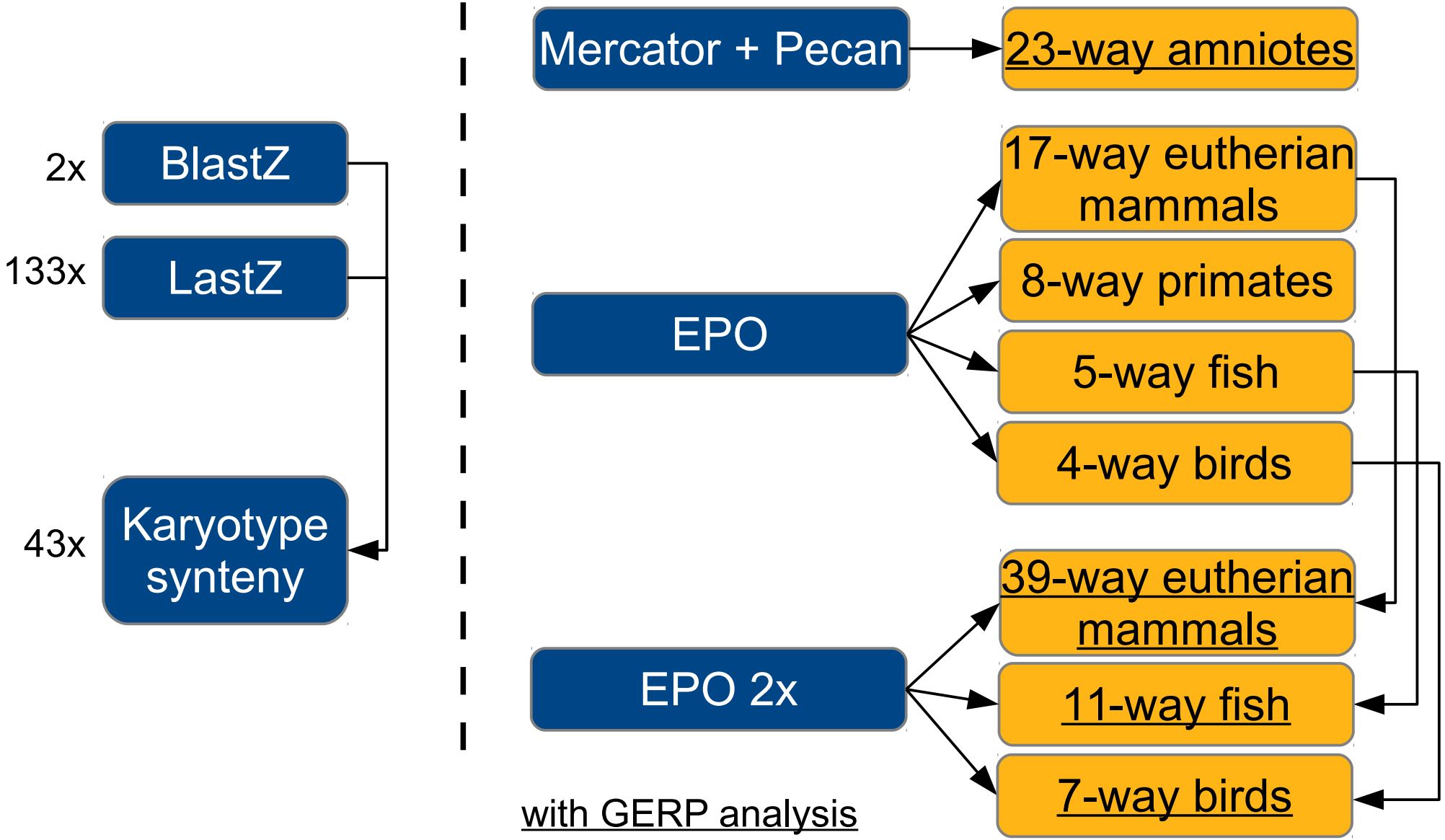
Gene trees (proteins, non-coding RNAs)

Gene orthology / paralogy predictions

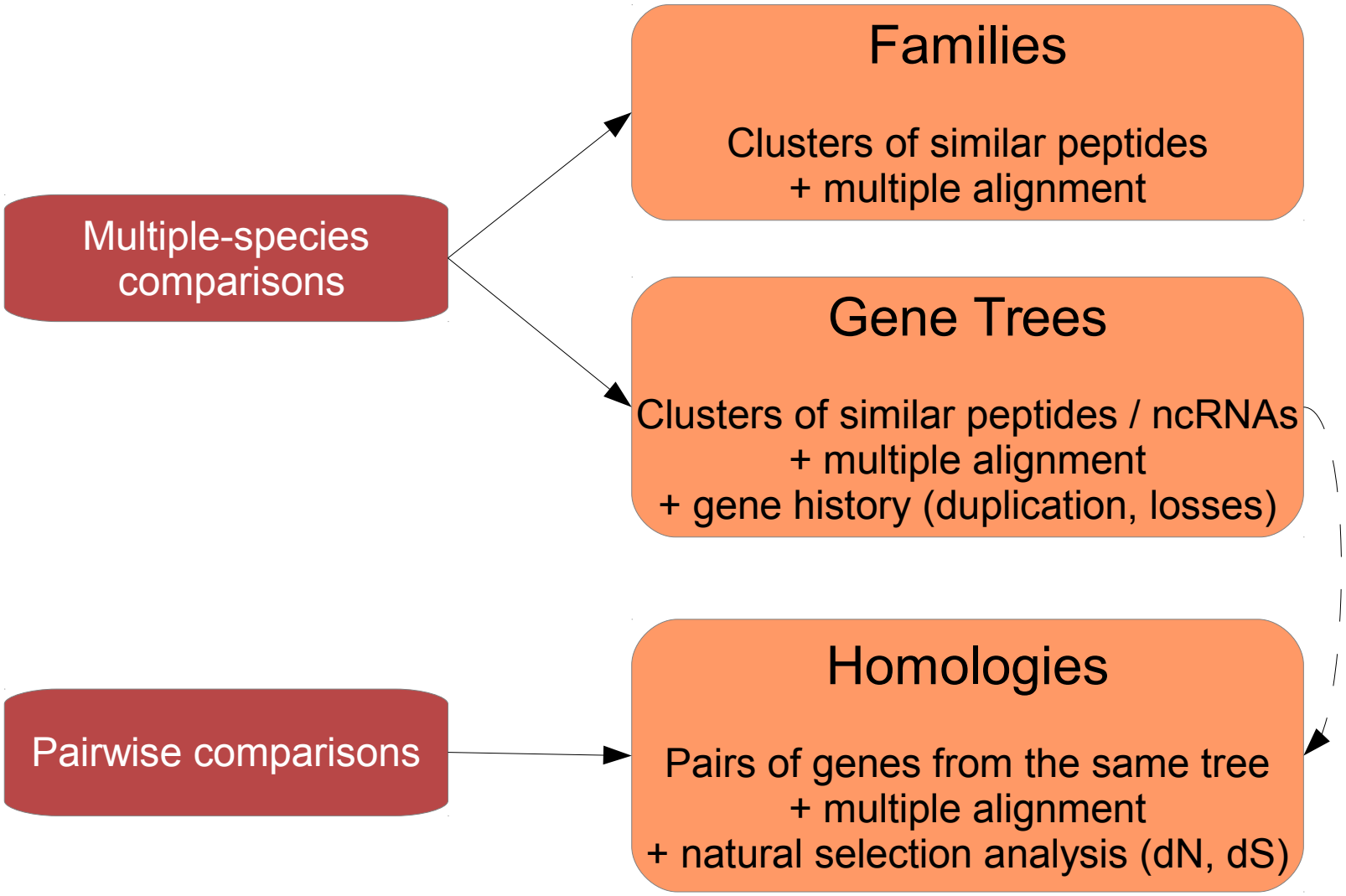
Nucleotide sequence analyses



Nucleotide sequence analyses in e!81



Gene analyses



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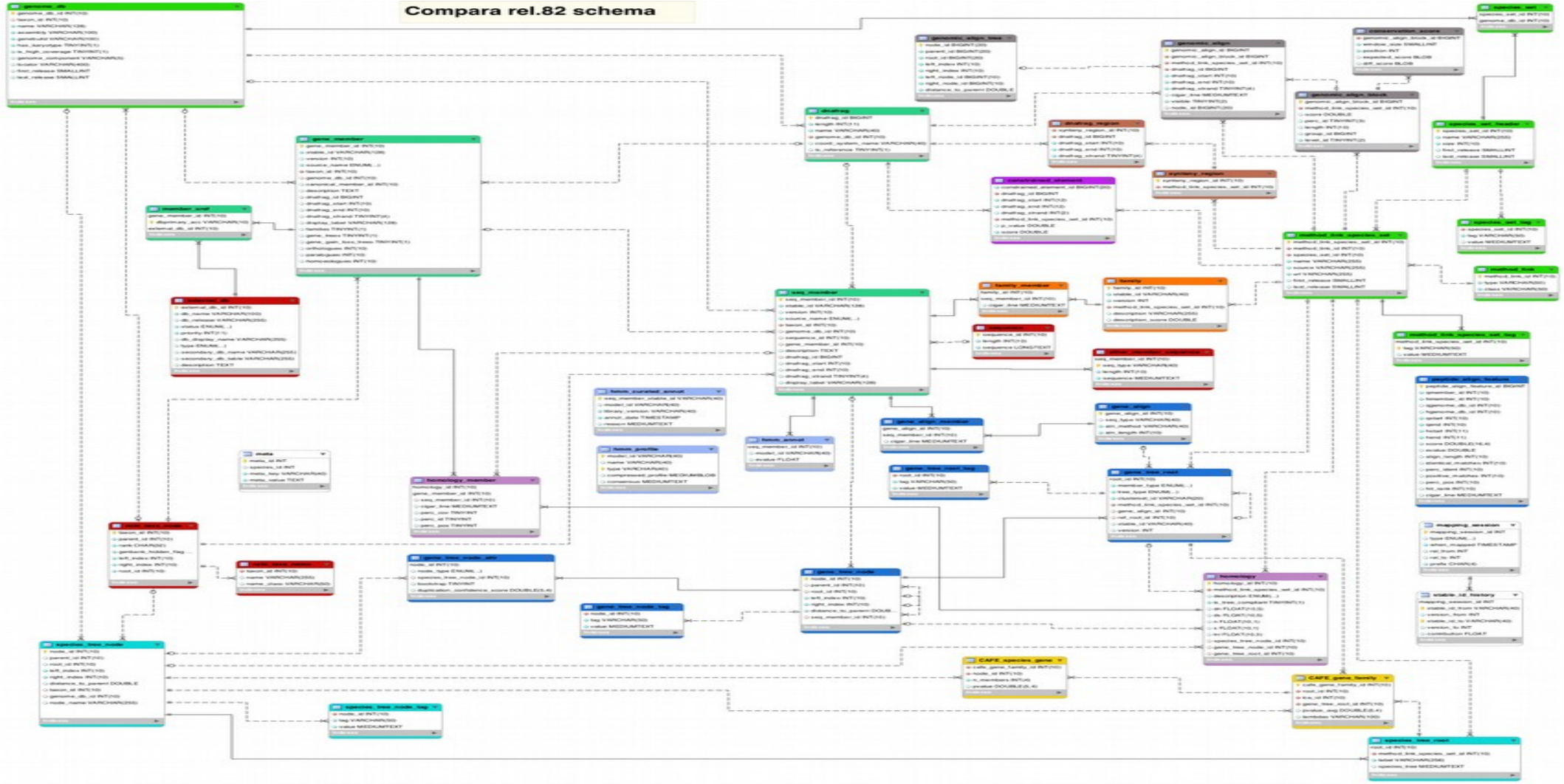
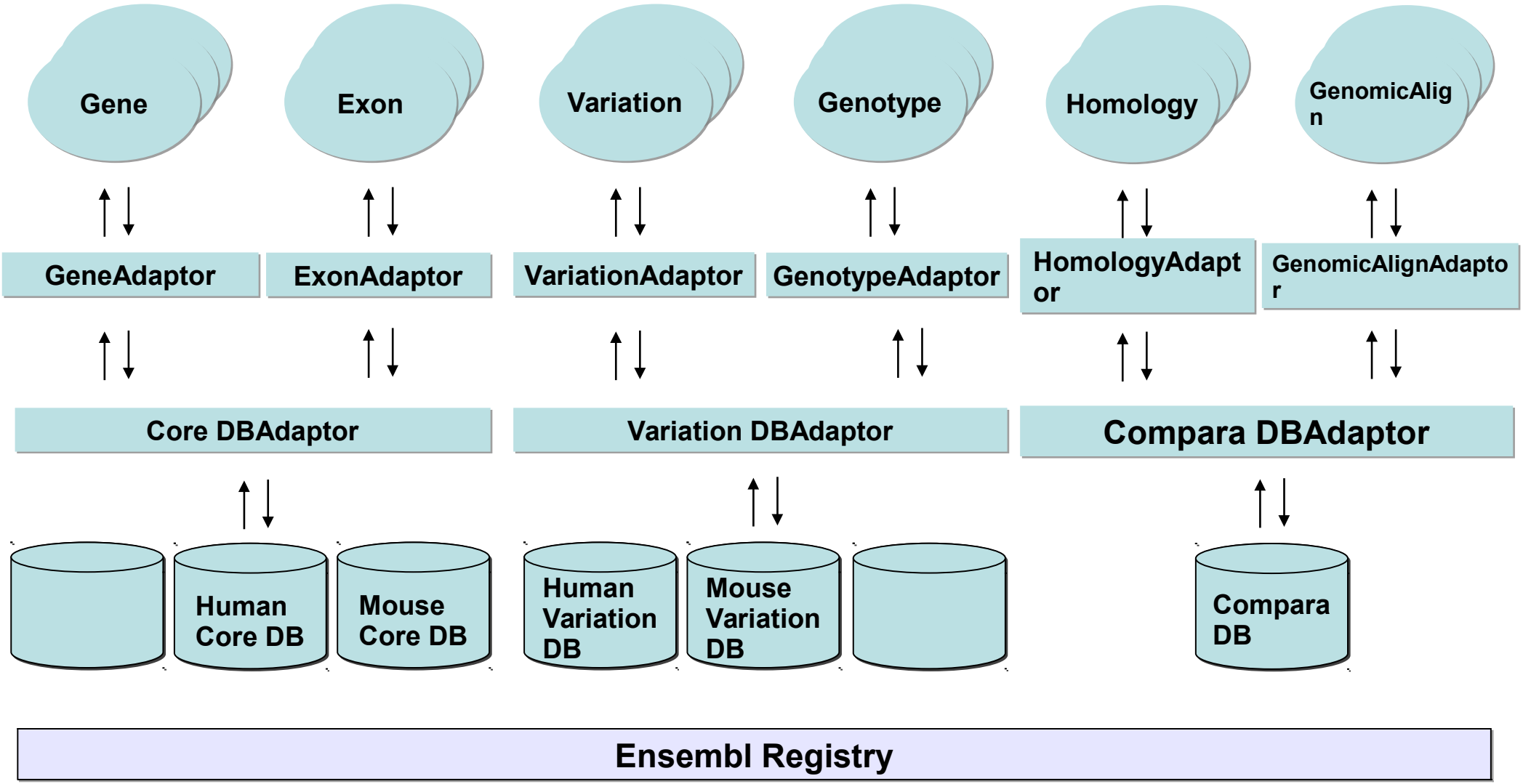
The Compara Perl API

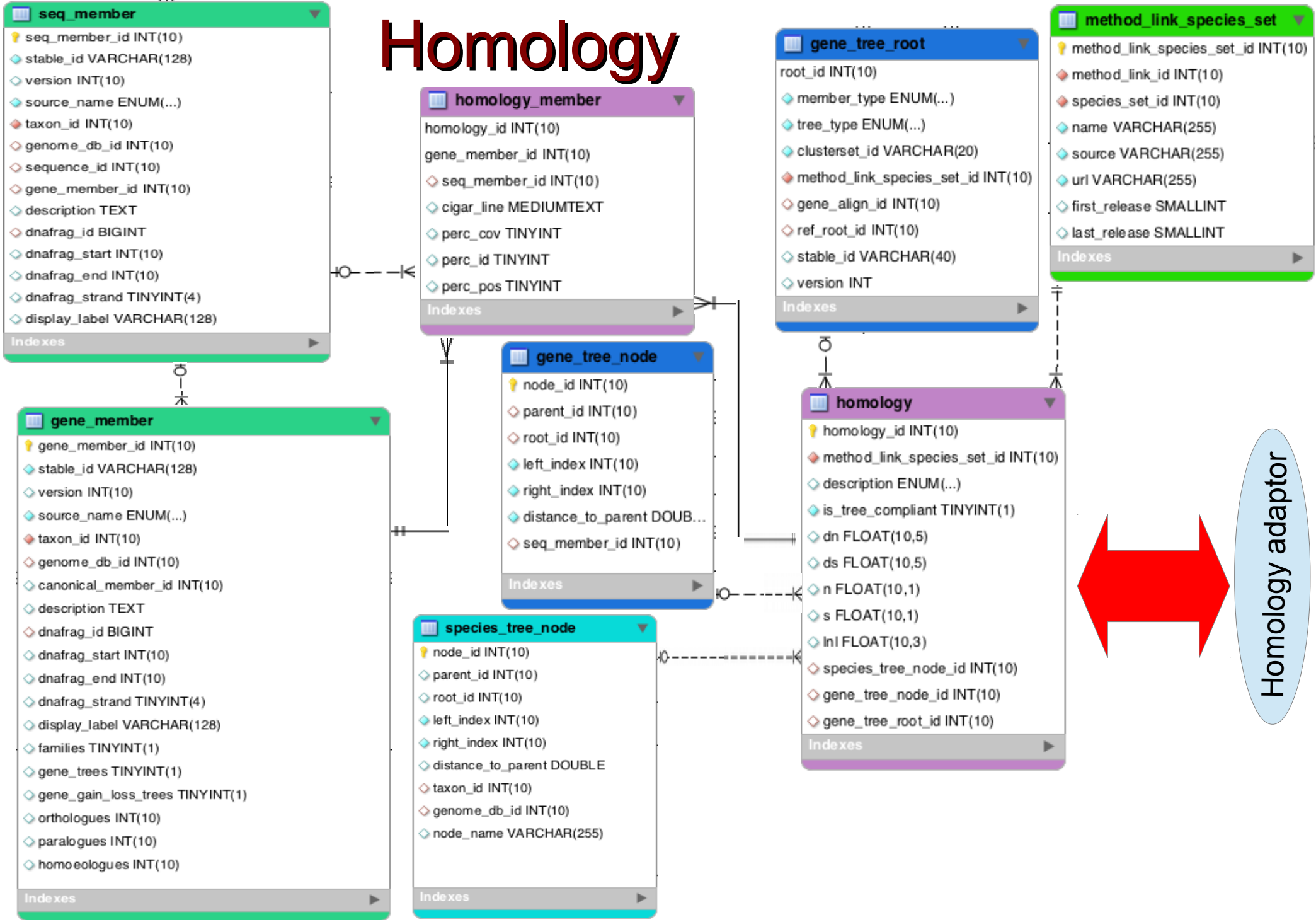
- Written in Object-Oriented Perl
- Used to retrieve data from and store data into the Ensembl Compara database
- Generalized to extend to non-Ensembl genomic data (Uniprot)
- Follows same ‘Object Adaptor’ & ‘Data Object’ design as the Core API


Compara rel.82 schema

Ensembl API Architecture



Homology


seq_member
seq_member_id INT(10)
stable_id VARCHAR(128)
version INT(10)
source_name ENUM(...)
taxon_id INT(10)
genome_db_id INT(10)
sequence_id INT(10)
gene_member_id INT(10)
description TEXT
dnafrag_id BIGINT
dnafrag_start INT(10)
dnafrag_end INT(10)
dnafrag_strand TINYINT(4)
display_label VARCHAR(128)
Indexes
homology_member
homology_id INT(10)
gene_member_id INT(10)
seq_member_id INT(10)
cigar_line MEDIUMTEXT
perc_cov TINYINT
perc_id TINYINT
perc_pos TINYINT
Indexes
gene_tree_root
root_id INT(10)
member_type ENUM(...)
tree_type ENUM(...)
clusterset_id VARCHAR(20)
method_link_species_set_id INT(10)
gene_align_id INT(10)
ref_root_id INT(10)
stable_id VARCHAR(40)
version INT
Indexes
method_link_species_set
method_link_species_set_id INT(10)
method_link_id INT(10)
species_set_id INT(10)
name VARCHAR(255)
source VARCHAR(255)
url VARCHAR(255)
first_release SMALLINT
last_release SMALLINT
Indexes
gene_tree_node
node_id INT(10)
parent_id INT(10)
root_id INT(10)
left_index INT(10)
right_index INT(10)
distance_to_parent DOUB...
seq_member_id INT(10)
Indexes
gene_member
gene_member_id INT(10)
stable_id VARCHAR(128)
version INT(10)
source_name ENUM(...)
taxon_id INT(10)
genome_db_id INT(10)
canonical_member_id INT(10)
description TEXT
dnafrag_id BIGINT
dnafrag_start INT(10)
dnafrag_end INT(10)
dnafrag_strand TINYINT(4)
display_label VARCHAR(128)
families TINYINT(1)
gene_trees TINYINT(1)
gene_gain_loss_trees TINYINT(1)
orthologues INT(10)
paralogues INT(10)
homoeologues INT(10)
Indexes
homology
homology_id INT(10)
method_link_species_set_id INT(10)
description ENUM(...)
is_tree_compliant TINYINT(1)
dn FLOAT(10,5)
ds FLOAT(10,5)
n FLOAT(10,1)
s FLOAT(10,1)
lnl FLOAT(10,3)
species_tree_node_id INT(10)
gene_tree_node_id INT(10)
gene_tree_root_id INT(10)
Indexes
species_tree_node
node_id INT(10)
parent_id INT(10)
root_id INT(10)
left_index INT(10)
right_index INT(10)
distance_to_parent DOUBLE
taxon_id INT(10)
genome_db_id INT(10)
node_name VARCHAR(255)
Indexes
Homology adaptor

Compara template script

```
use strict;
use Bio::EnsEMBL::Registry;
my $reg = "Bio::EnsEMBL::Registry";

# Auto-configure the registry
$reg->load_registry_from_db(
    -host => "ensembldb.ensembl.org",
    -user => "anonymous"
);


# Get the adaptor object for the data type you want
# e.g. GeneTree
my $xx_adaptor =  $reg->get_adaptor("Multi", "compara", "XX");


# Fetch the data objects using the adaptor
# e.g. get all the genes in a given gene tree
my $all_interesting_xx = $xx_adaptor->fetch_all_by_YY();


print "All XX objects from E!Compara :\n";
foreach my $this_xx (@$all_interesting_xx) {
  # Do some stuff with the data object
  print "\t", $this_xx->stable_id, "\n";
}
```

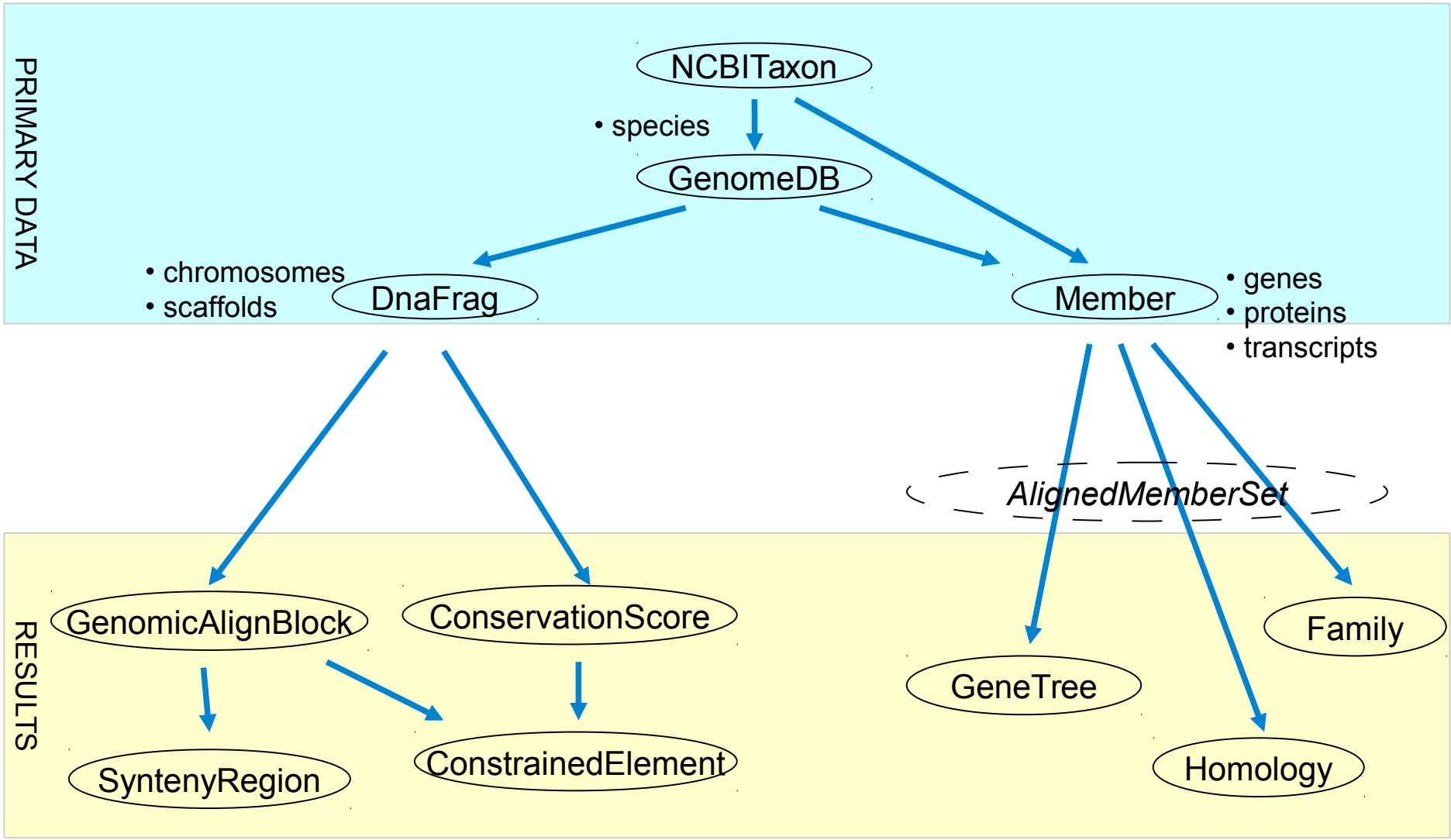
Help & Useful documentation

- perldoc – Viewer for offline API documentation
  - `shell> perldoc Bio::EnsEMBL::Compara::GenomeDB`
  - `shell> perldoc Bio::EnsEMBL::Compara::DBSQL::DnaFragAdaptor`

- Online documents (website)
  - http://e81.ensembl.org/info/docs/Doxygen/compara-api/index.html
  - http://e81.ensembl.org/info/docs/api/compara/index.html

- Mailing lists:
  - dev@ensembl.org
  - helpdesk@ensembl.org

Compara object model overview



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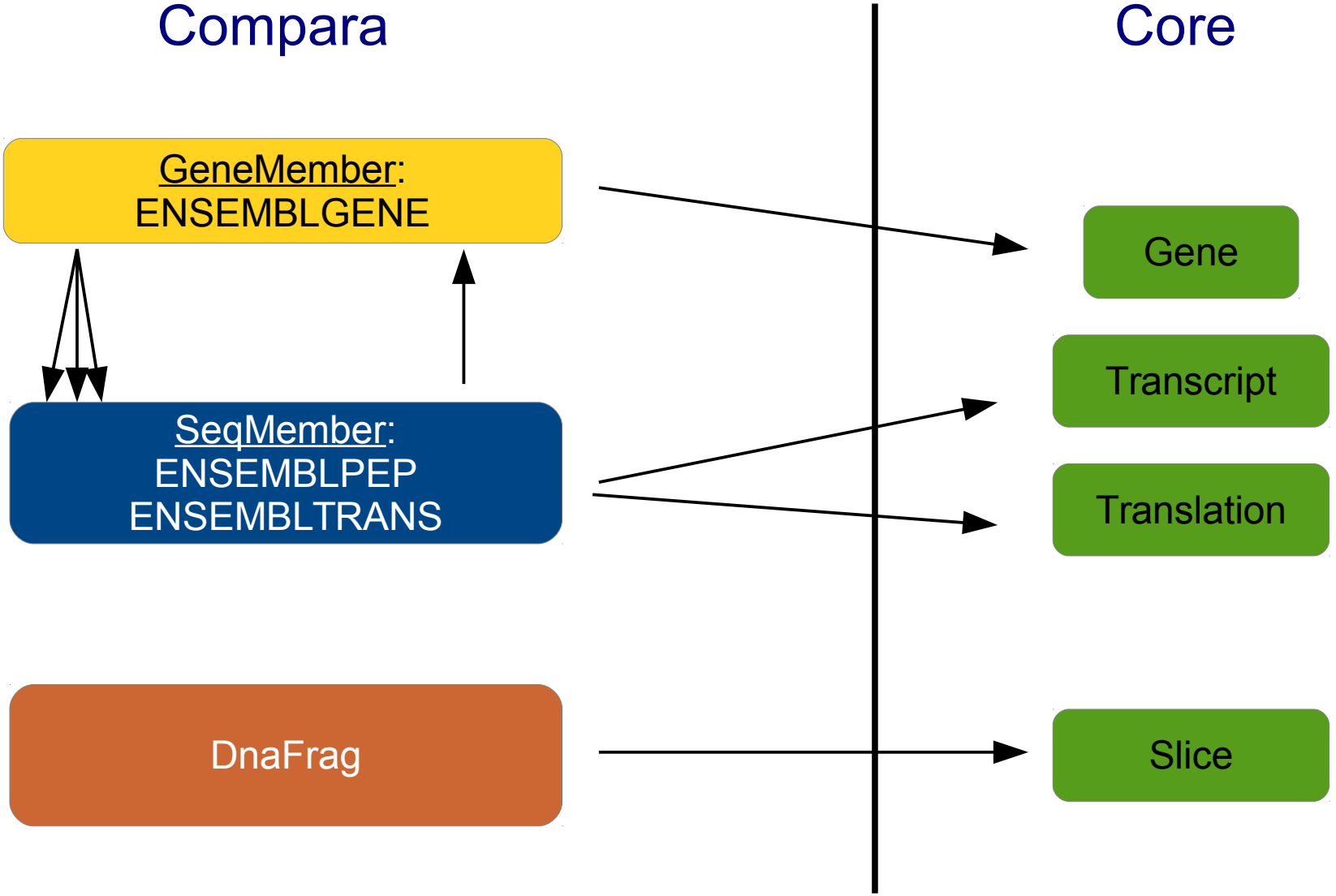
Links between Compara and Core

- Compara only stores references to the Core objects
- The full data lies in the core databases

Links between Compara and Core



GenomeDB

- Represents a species
  Links the Compara database to the Core species databases

Attributes	Methods
Species name	`$genomedb->name()`
Assembly	`$genomedb->assembly()`
Gene build	`$genomedb->genebuild()`
Taxon	`$genomedb->taxon_id()`
Adaptor methods	
`$genomedb_adaptor->fetch_all(...)`	
`$genomedb_adaptor->fetch_by_registry_name(...)`	

DnaFrag

- Represents a top-level region in the Compara database.
- Equivalent to a whole-sequence Slice

Attributes	Methods
Region name	*$dnafrag->name()*
Region type	*$dnafrag->coord_system_name()*
Adaptor methods	
`$dnafrag_adaptor->fetch_all_by_GenomeDB_region(...)`	
`$dnafrag_adaptor->fetch_by_Slice(...)`	
`$nafrag_adaptor->fetch_by_GenomeDB_and_name(...)`	

Code Examples

1. GenomeDB

```
my $genome_db_adaptor = Bio::EnsEMBL::Registry->get_adaptor( "Multi", "compara", "GenomeDB");
my $list_ref_of_gdbs = $genome_db_adaptor->fetch_all();

foreach my $genome_db( @{ $list_ref_of_gdbs } ){
   print join( "\t", $genome_db->dbID(), $genome_db->name(), $genome_db->assembly() ), "\n";
}
```

2. DnaFrag

```
my $dnafrag_adaptor = $reg->get_adaptor("Multi", "compara", "DnaFrag");
my $gorilla_chr_dnafrags = $dnafrag_adaptor-
>fetch_all_by_GenomeDB_region( $gorilla_genome_db, 'chromosome' );

foreach my $dnafrag (@{ $gorilla_chr_dnafrags }){
   print "Chromsome ", $dnafrag->name(), " contains ", $dnafrag->length(), " bp.\n";
}
```

Exercises – GenomeDB & DnaFrag

- Print the name, assembly version and genebuild version for all the GenomeDBs in the compara database

- Print all the chromosomes (DnaFrags) for chimpanzee

GeneMember and *SeqMember*

- GeneMember for genes
  - source_name: ENSEMBLGENE
- SeqMember for RNAs and proteins
  - source_name: ENSEMBLPEP, ENSEMBLTRANS, Uniprot/SPTREMBL, Uniprot/SWISSPROT

Attributes	Methods
Stable ID	`$member->stable_id()`
Coordinates	`$member->chr_name()` `$member->chr_start()` …
Sequence (SeqMember only)	`$member->sequence()`
Function	`$member->description()`
Adaptor methods	
`$seq_member_adaptor->fetch_by_stable_id(…)`	
`$gene_member_adaptor->fetch_all_by_GenomeDB(…)`	

HOWTO: get an Ensembl ID from a gene symbol

- Compara only references genes by their Ensembl stable ID
- From a gene symbol, you first have to use the core API to get the stable id(s)
- Gene symbols may not be unique (for instance: U6)

```
# Get the Human gene adaptor
my $hg_adaptor = $reg->get_adaptor("human", "core", "Gene");

# Get all the genes
my $all_genes = $hg_adaptor->fetch_all_by_external_name(XX);

# For each gene
foreach my $gene (@{$all_genes}) {
   do some stuff with $gene->stable_id();
}
```

Code Example - Member

```
my $seq_member_adaptor = $reg->get_adaptor("Multi", "compara", "SeqMember");
my $human_seq_members =
                    $seq_member_adaptor->fetch_all_by_GenomeDB($gorilla_genome_db);

# print 10 peptide members and 10 transcript members
my ($pep_count, $trans_count) = (0, 0);
foreach my $seq_mem ( @{ $human_seq_members } ) {
   my $type = $seq_mem->source_name();
   if ( $type =~ m/PEP/ && $pep_count < 10 ){
      print $seq_mem->stable_id(), ":", $seq_mem->source_name(), "\n";
      $pep_count++;
   }
   elsif ( $type =~ m/TRANS/ && $trans_count < 10 ){
      print $seq_mem->stable_id(), ":", $seq_mem->source_name(), "\n";
      $trans_count++;
   }
   elsif ( $pep_count >= 10 && $trans_count >= 10 ) {
      last;
   }
}
```

Exercises - *Member*

- Print the sequence of the Member corresponding to SwissProt protein O93279

- Find and print the sequence of all the peptide Members corresponding to the human protein-coding gene(s) FRAS1

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AlignedMemberSet object

- Base object that represents a set of members aligned together, e.g. a multiple alignment of peptides / ncRNAs
- “Applied” in gene trees, families, and homologies
- No specific adaptor

Attributes	Methods
List of members	`$aln->get_all_Members()` `$aln->get_all_GeneMembers()`
Alignment (BioPerl object)	`$aln->get_SimpleAlign()`
Description (if available)	`$aln->description()`
Stable ID (if available)	`$aln->stable_id()`

HOWTO: print a BioPerl alignment

- Compara objects return alignments as BioPerl instances

```
$aln->get_SimpleAlign()
```

- BioPerl provides an AlignIO object to format the actual output in various formats (fasta, clustalw, phylip …)

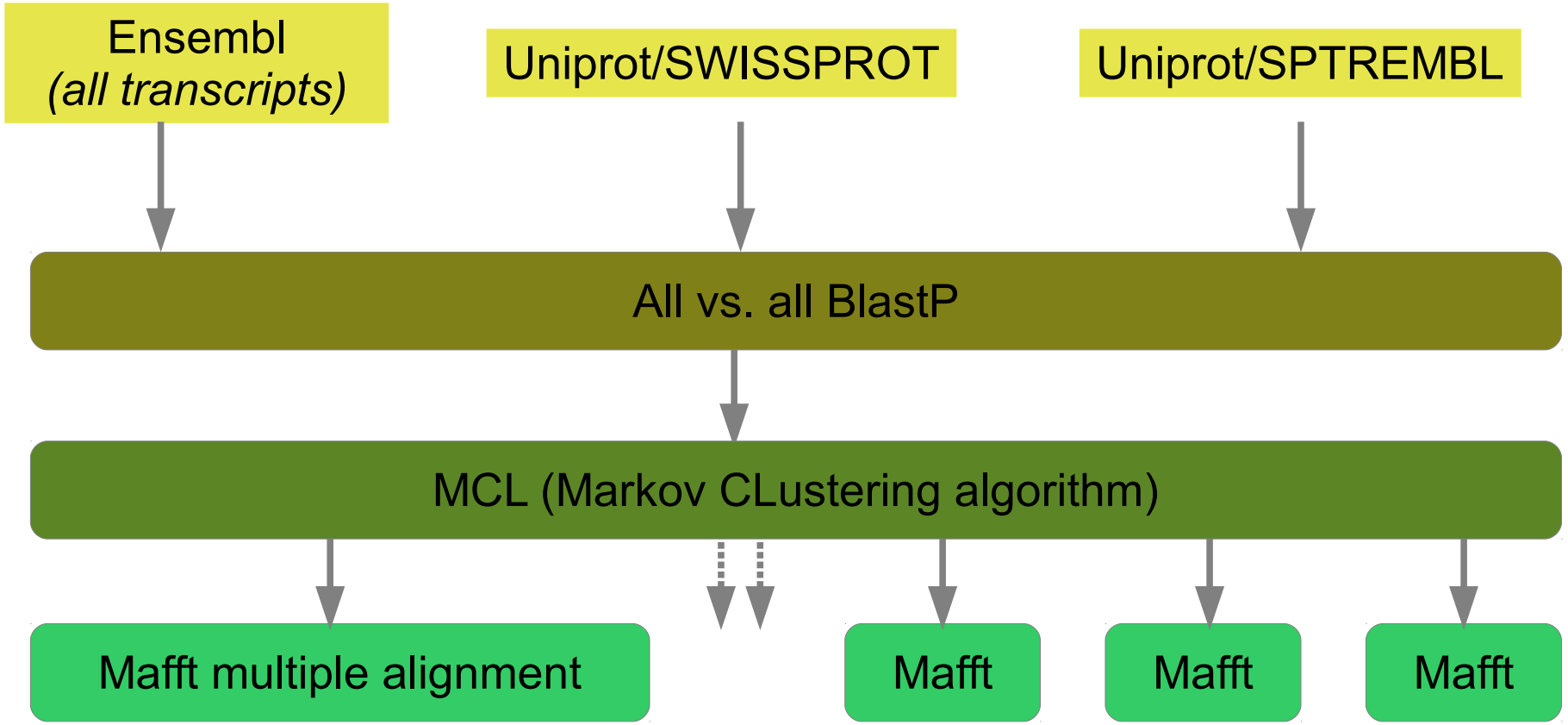
```
use Bio::AlignIO;

# Get the alignIO object from BioPerl
my $alignIO = Bio::AlignIO->newFh(-format => "fasta");

# Print the alignment
print $alignIO $aln;
```

Families

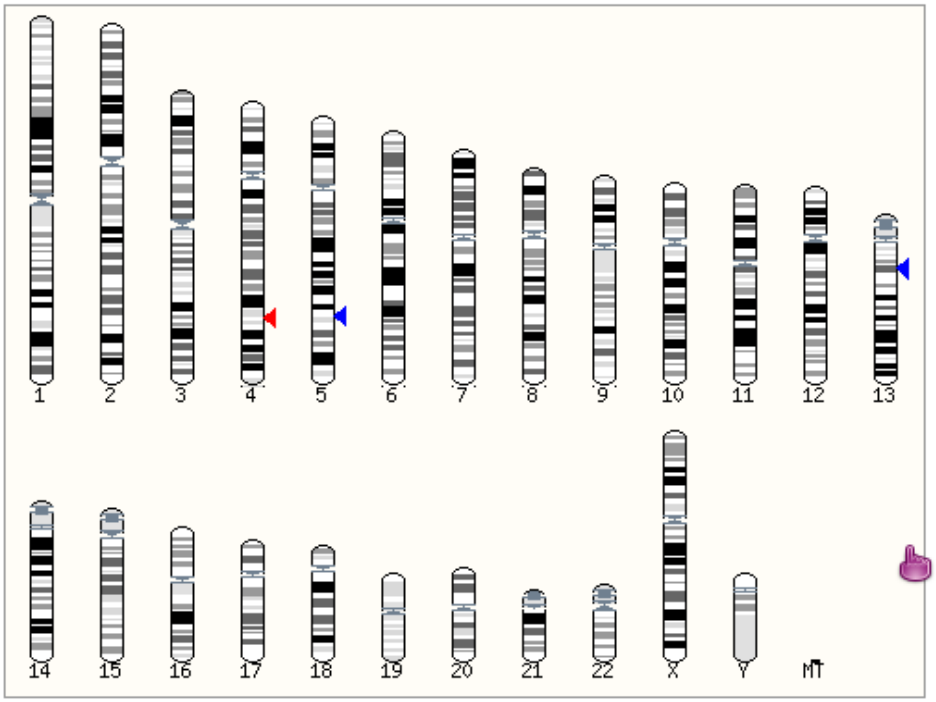
Families are clusters of similar peptides



Example on the web: ENSFM00750001632338 in Human

HUMAN genes in this family

Ensembl genes containing proteins in family ENSFM00750001632338



Gene ID and Location	Gene Name	Description (if known)
ENSG00000170365 Chromosome 4: 146.40m	SMAD1	SMAD family member 1 [Source:HGNC Symbol;Acc:6767]
ENSG00000113658 Chromosome 5: 135.47m	SMAD5	SMAD family member 5 [Source:HGNC Symbol;Acc:6771]
ENSG00000120693 Chromosome 13: 37.42m	SMAD9	SMAD family member 9 [Source:HGNC Symbol;Acc:6774]

Family object

- (almost) the same methods as in *AlignedMemberSet*
- Alternative transcripts can belong to different families !

Attributes	Methods
Alignment	`$family->get_SimpleAlign()`
Biological function	`$family->description()`
Gene content	`$family->get_all_Members()`
Adaptor methods	
`$family_adaptor->fetch_all_by_GeneMember(…)` `$family_adaptor->fetch_by_SeqMember(…)`	
`$family_adaptor->fetch_by_stable_id(…)`	

Code Example - Family

```
my $family_adaptor = $reg->get_adaptor("Multi", "compara", "Family");
my $ddx_families = $family_adaptor-
>fetch_by_description_with_wildcards('dead box', 1);

# print first 10 family descriptions
my $c = 0;
foreach my $fam ( @{ $ddx_families } ) {
   print $fam->description(), "\n";
   $c++;
   last if $c >= 10;
}
```

Exercises - Families

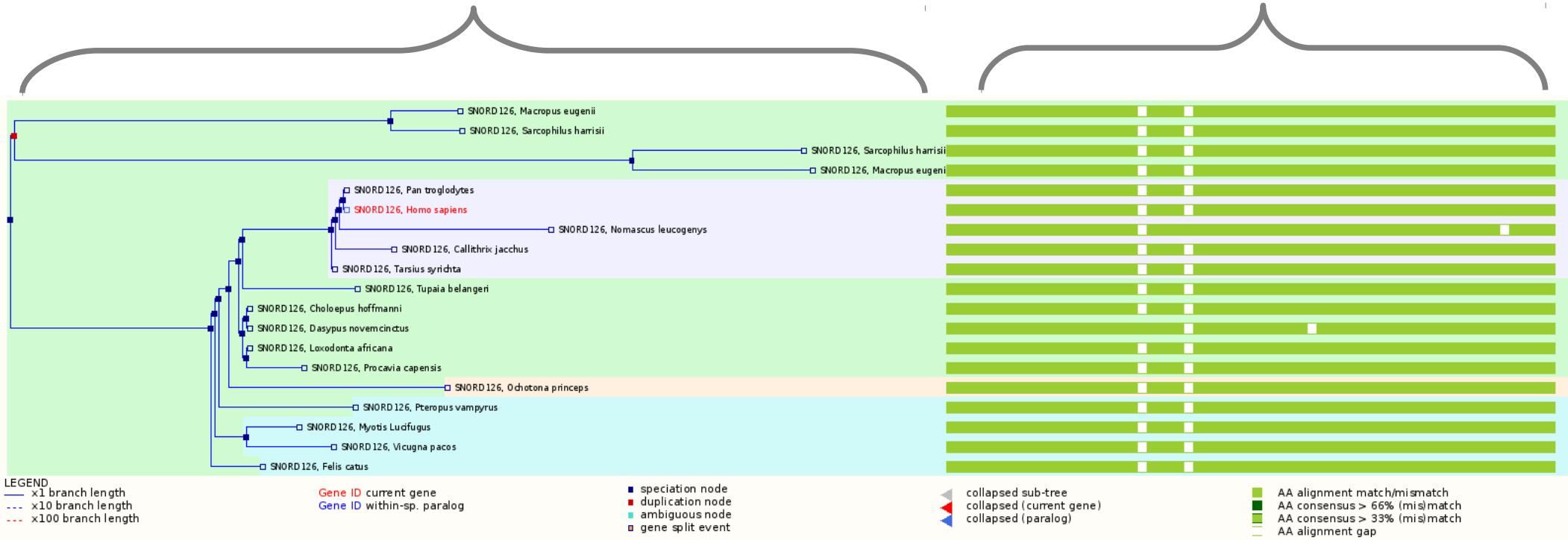
- Get the multiple alignment corresponding to the family with the stable id ENSFM00250000006121

- Get the families predicted for the human gene ENSG00000139618. What do you notice ?

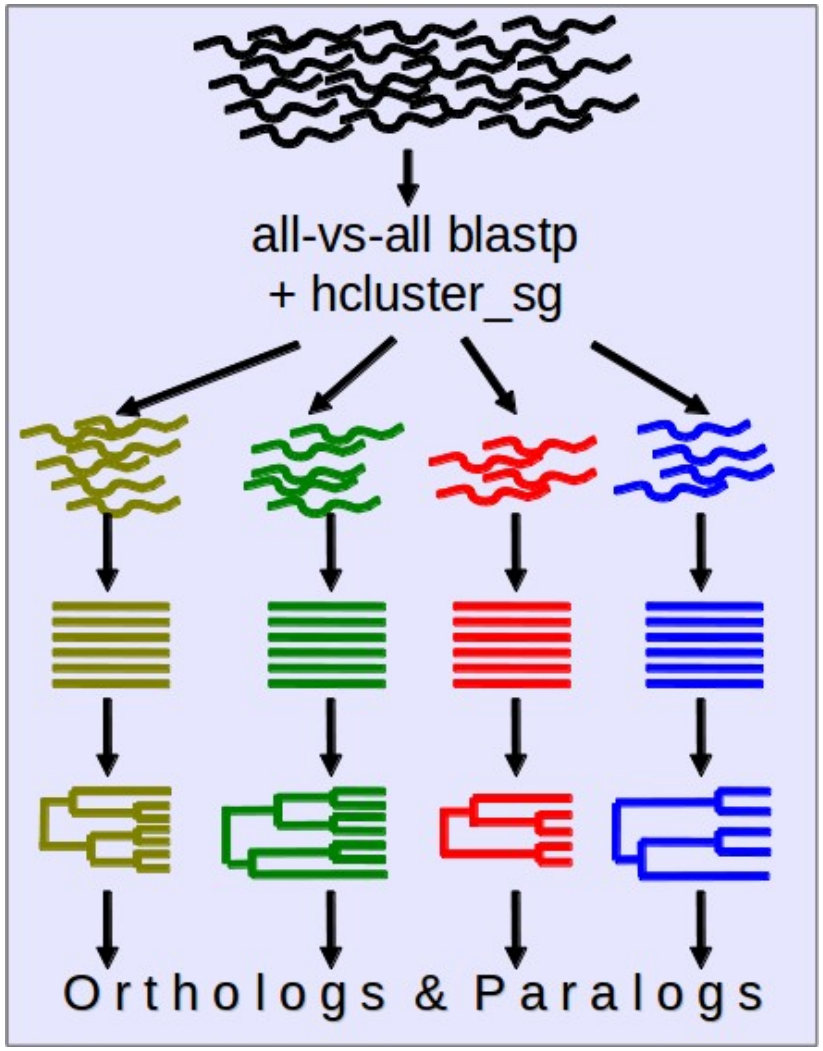
GeneTree example on the website

Tree

Multiple alignment



Protein-Tree pipeline overview



All *e!* genes – canonical prot.

BLAST

hcluster_sg

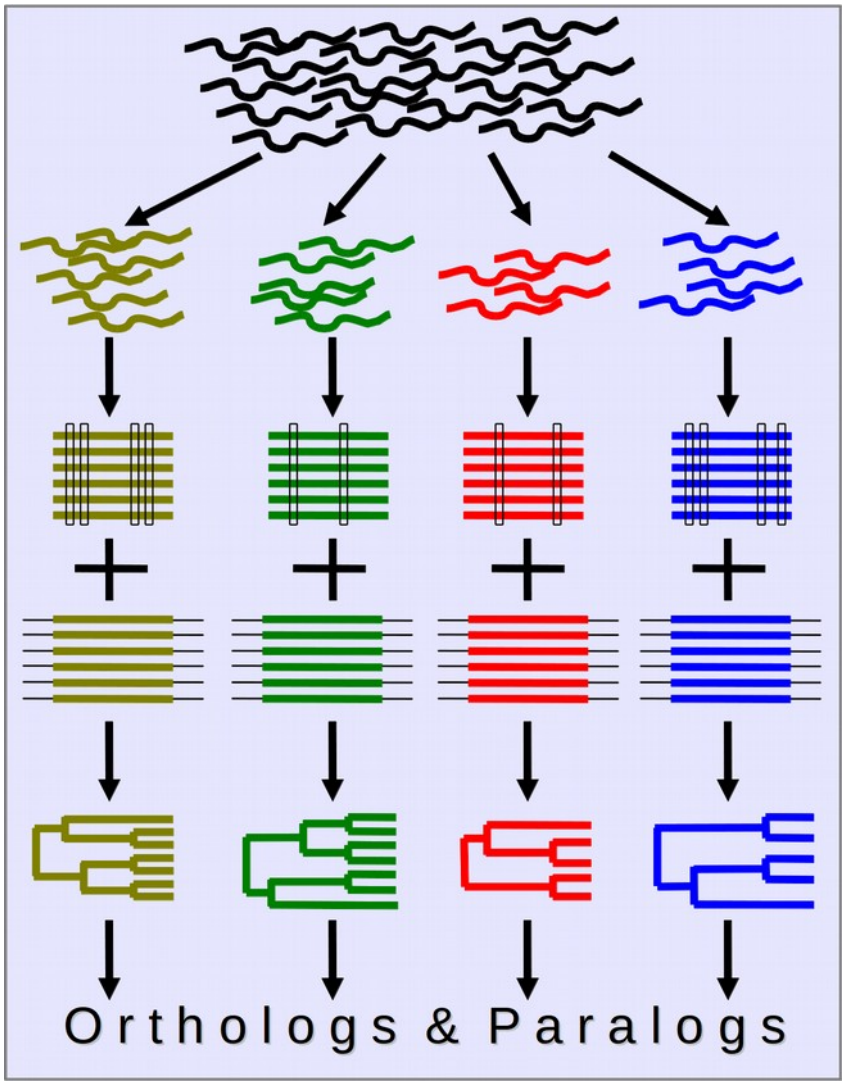
MCoffee: MSA

TreeBeST: (+ reconciliation)

Ortholog/Paralog inference

Vilella et al., Genome Res. 2009

ncRNA-Tree pipeline overview



All *e!* ncRNA genes

Grouped in Family Models - RFAM

Infernal alignment + RaxML trees

PRANK alignment + NJ/ML trees

TreeBeST (tree reconciliation)

Ortholog/Paralog inference

Pignatelli et al., in preparation

GeneTree object

- *fetch_all** methods may require some more arguments:

```
-clusterset_id => 'default'
-tree_type => 'tree'
-member_type => 'protein' or 'ncrna'
```

Attributes	Methods
Alignment	*$family->get_SimpleAlign()*
Tree export	*$tree->newick_format('simple')* *$tree->nhx_format('full')* *$tree->print_tree()*
Stable ID	*$tree->stable_id()*
Adaptor methods	
`$genetree_adaptor->fetch_by_stable_id(…)`	
`$genetree_adaptor->fetch_default_for_Member(…)`	

Exercises – Protein and ncRNA trees

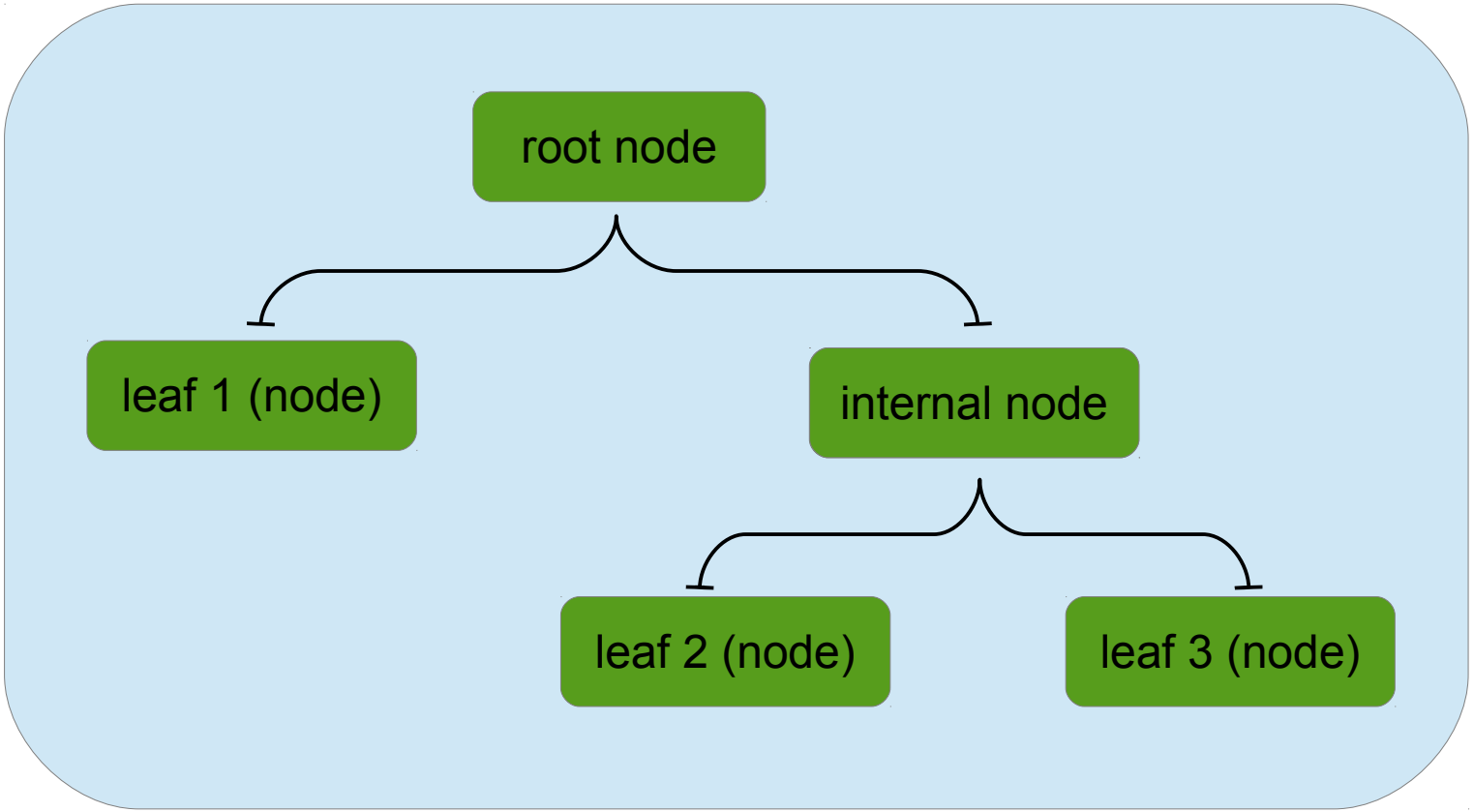
- Print the protein tree with the stable id ENSGT00390000003602

- Print all the members of the tree containing the human ncRNA gene ENSG00000238344, and their alignment

GeneTreeNode object

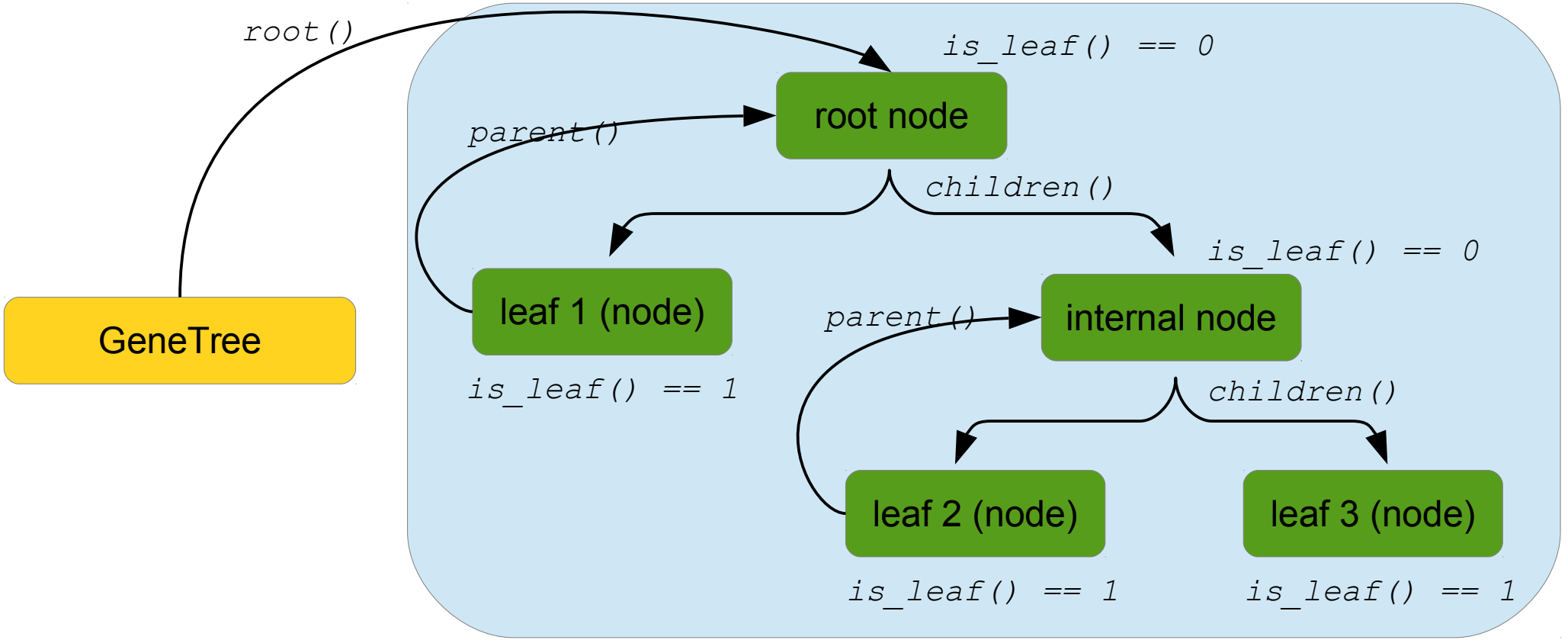
The actual tree structure is a hierarchy of *GeneTreeNode* objects

GeneTree



GeneTreeNode object

The actual tree structure is a hierarchy of *GeneTreeNode* objects



Extra information

```
$node->node_type()                  $node->duplication_confidence_score()
$node->taxonomy_level()             $node->bootstrap()
```

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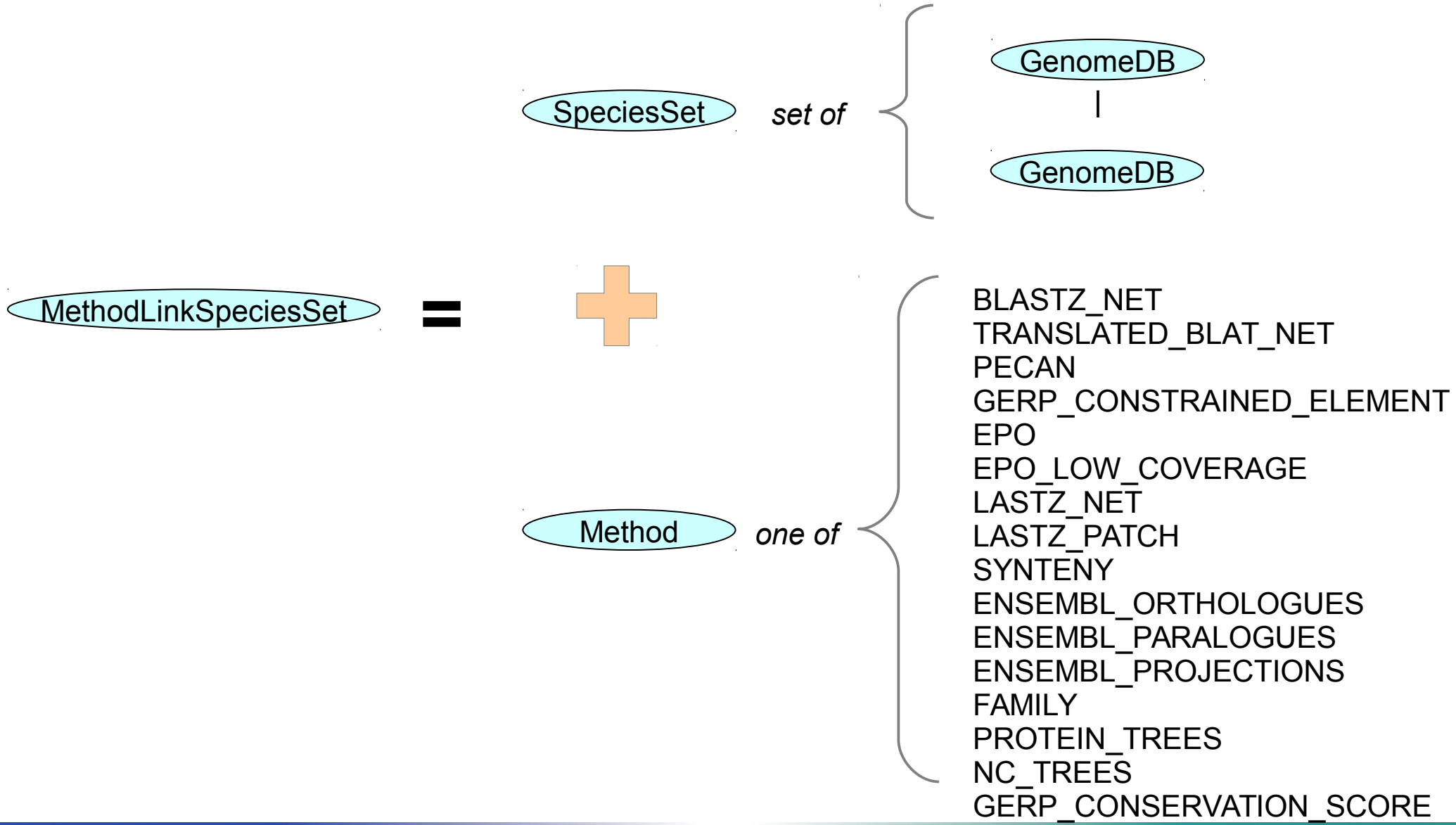
MethodLinkSpeciesSet object

- The Compara database contains **lots** of cross-species comparisons
- There are multiple comparisons of the same type (pairwise alignments, homologies, etc)
- We need a way of defining which analysis is performed on which genomes
- Many adaptor methods require a MethodLinkSpeciesSet

MethodLinkSpeciesSet object



MethodLinkSpeciesSet

- Links a method (an analysis) to a set of species

Attributes	Methods
Name	*$mlss->name()*
Type of analysis	*$mlss->method()->type()*
List of GenomeDBs	*$mlss->species_set()*
Adaptor methods	
`$mlss_adaptor->fetch_by_method_link_type_registry_aliases()`	
`$mlss_adaptor->fetch_by_method_link_type_species_set_name()`	

Example Code – MethodLinkSpeciesSet

```
my $gdb_a = $reg->get_adaptor( "Multi", "compara", "GenomeDB" );
my $gorilla_genome_db = $gdb_a->fetch_by_dbID(123);

my $mlss_adaptor = $reg->get_adaptor("Multi", "compara", "MethodLinkSpeciesSet");
my $gorilla_mlss_list = $mlss_adaptor->fetch_all_by_GenomeDB( $gorilla_genome_db );

my $c = 0;
foreach my $mlss ( @{ $gorilla_mlss_list } ) {
   print join( "\t", $mlss->dbID(), $mlss->method->type() ), "\n";
   $c++;
   last if $c >= 10;
}
```

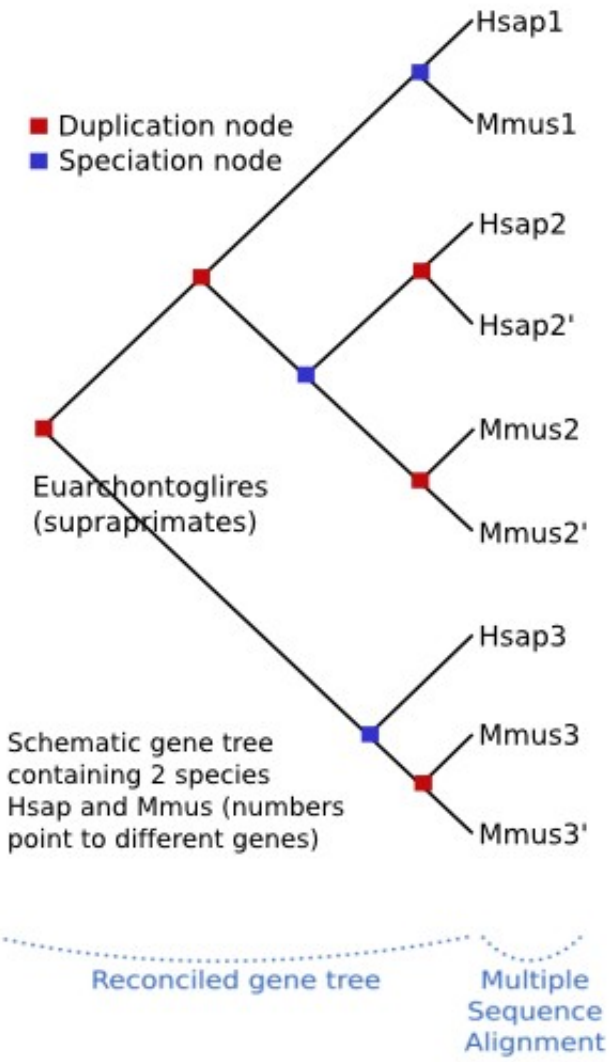
Exercises – MethodLinkSpeciesSet

- Print the total number of MethodLinkSpeciesSet entries stored in the database

- Print a unique list of method_link_types and a count of their number in the database.

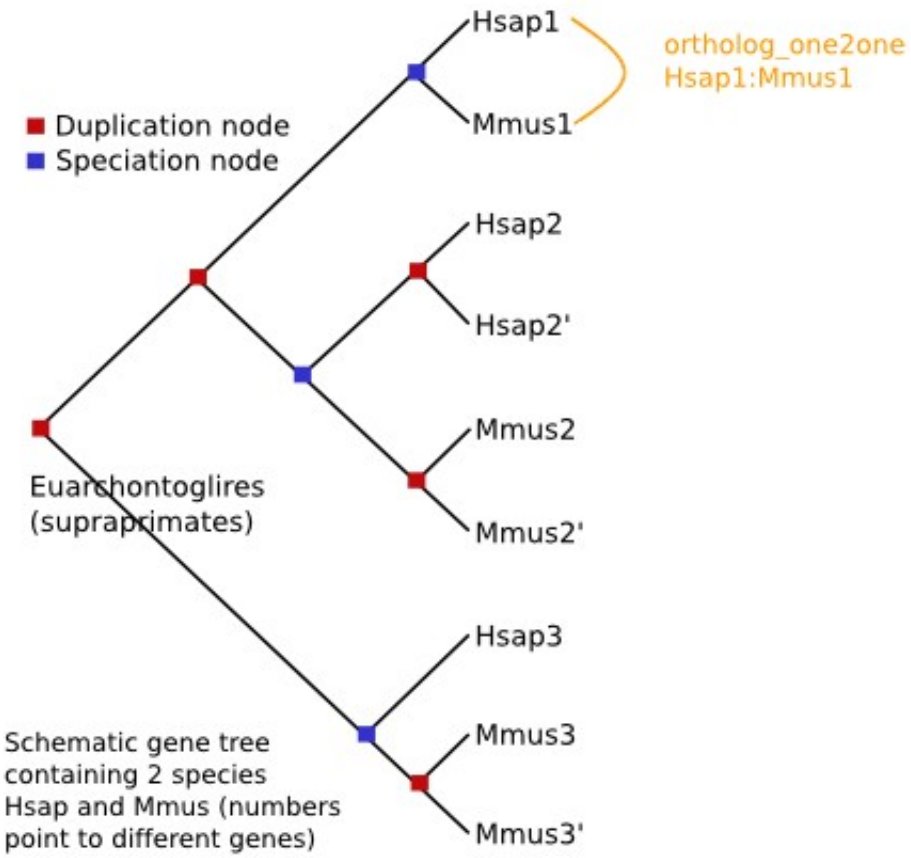
- Print the list of the species for the 17 eutherian mammals EPO alignments

Homology inference

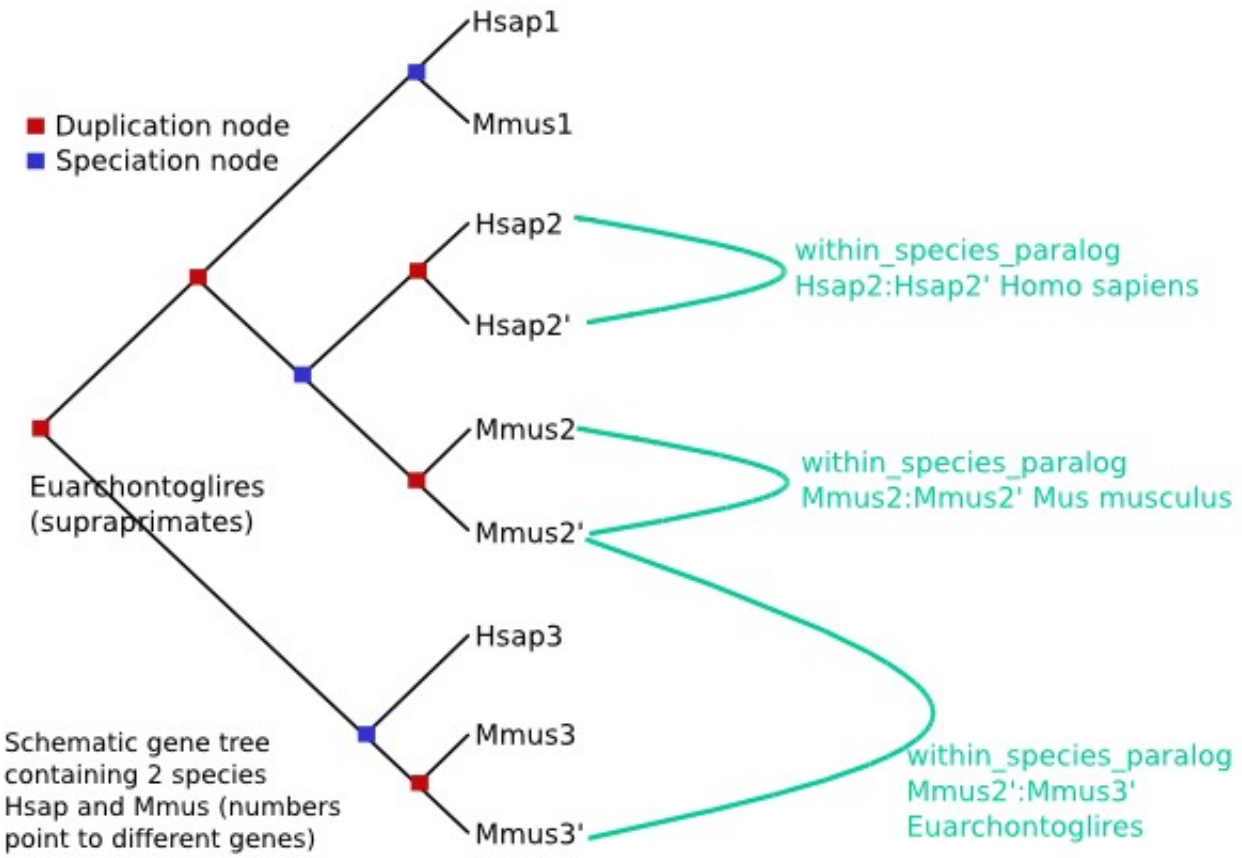


Consists in tagging the pairs of genes of all the trees with a relation type, depending on the tree topology.

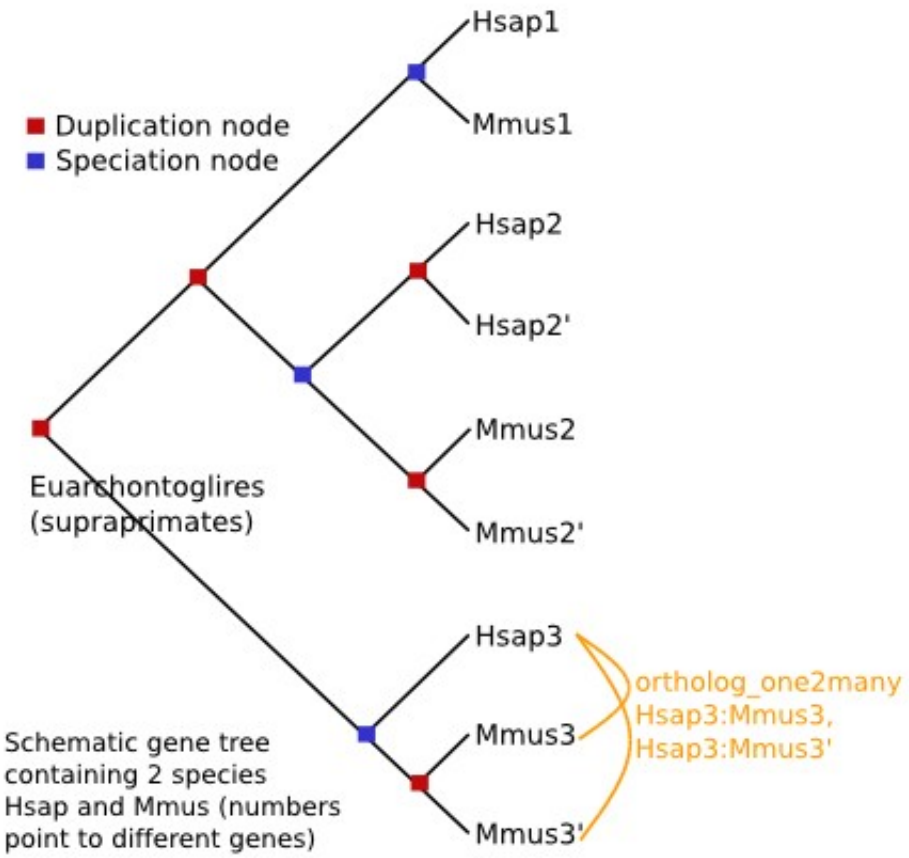
Homology inference



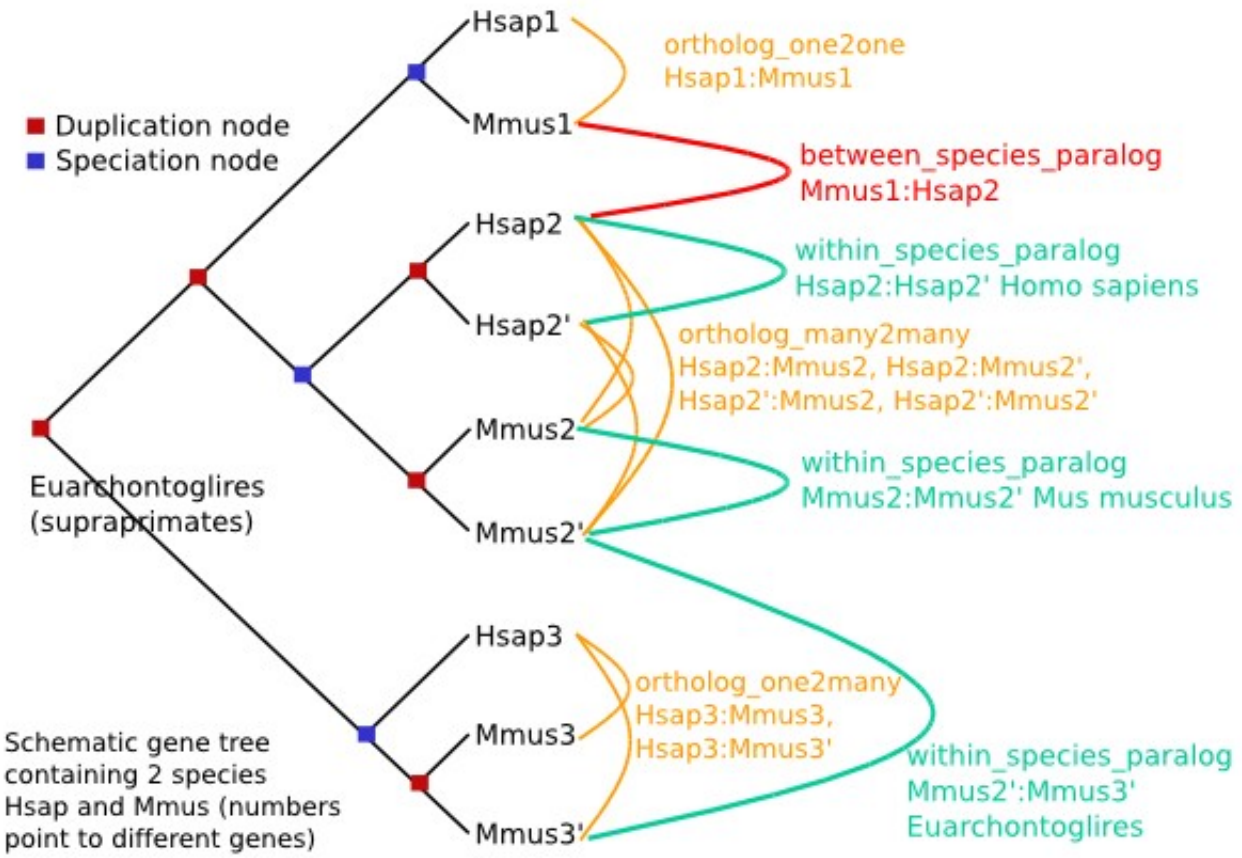
Homology inference



Homology inference



Homology inference



Homology object

- An Homology object links two genes together
- One-to-many relationships are split:
  - "H ortholog to M1" and "H ortholog to M2" are different objects

Attributes	Methods
Alignment	*$homology->get_SimpleAlign()*
Natural selection	*$homology->dn() / $homology->ds()*
Gene content	*$homology->get_all_GeneMembers()*
Homology characteristics	*$homology->description()* *$homology->taxonomy_level()*
Adaptor methods	
`$homology_adaptor->fetch_all_by_Member(…)`	
`$homology_adaptor->fetch_all_by_MethodLinkSpeciesSet(…)`	
`$homology_adaptor->fetch_all_by_Member_paired_species(…)`	

Code Example - Homology

```
my ( $human_genomedb_id, $gorilla_genomedb_id ) = ( 150, 123 );

my $mlss_adaptor = $reg->get_adaptor("Multi", "compara", "MethodLinkSpeciesSet");
my $homology_adaptor = $reg->get_adaptor("Multi", "compara", "Homology");

my $mlss = $mlss_adaptor->fetch_by_method_link_type_genome_db_ids(
      'ENSEMBL_ORTHOLOGUES',
      [$human_genomedb_id, $gorilla_genomedb_id]
);
my $orthologs = $homology_adaptor->fetch_all_by_MethodLinkSpeciesSet($mlss);

my $c = 0;
foreach my $orth ( @{ $orthologs } ){
   print $orth->toString(), "\n" if $orth->is_tree_compliant();
   $c++;
   last if $c >= 10;
}
```

Exercises – Homologies (and MethodLinkSpeciesSet)

- Get all the homologues for the human gene ENSG00000229314
- Count the number of “one2one” homologues between human and mouse
- Find the human orthologues of ENSMUSG00000004843 and ENSMUSG00000025746. For each homology, display the alignment and the dn value. Comment on the divergence

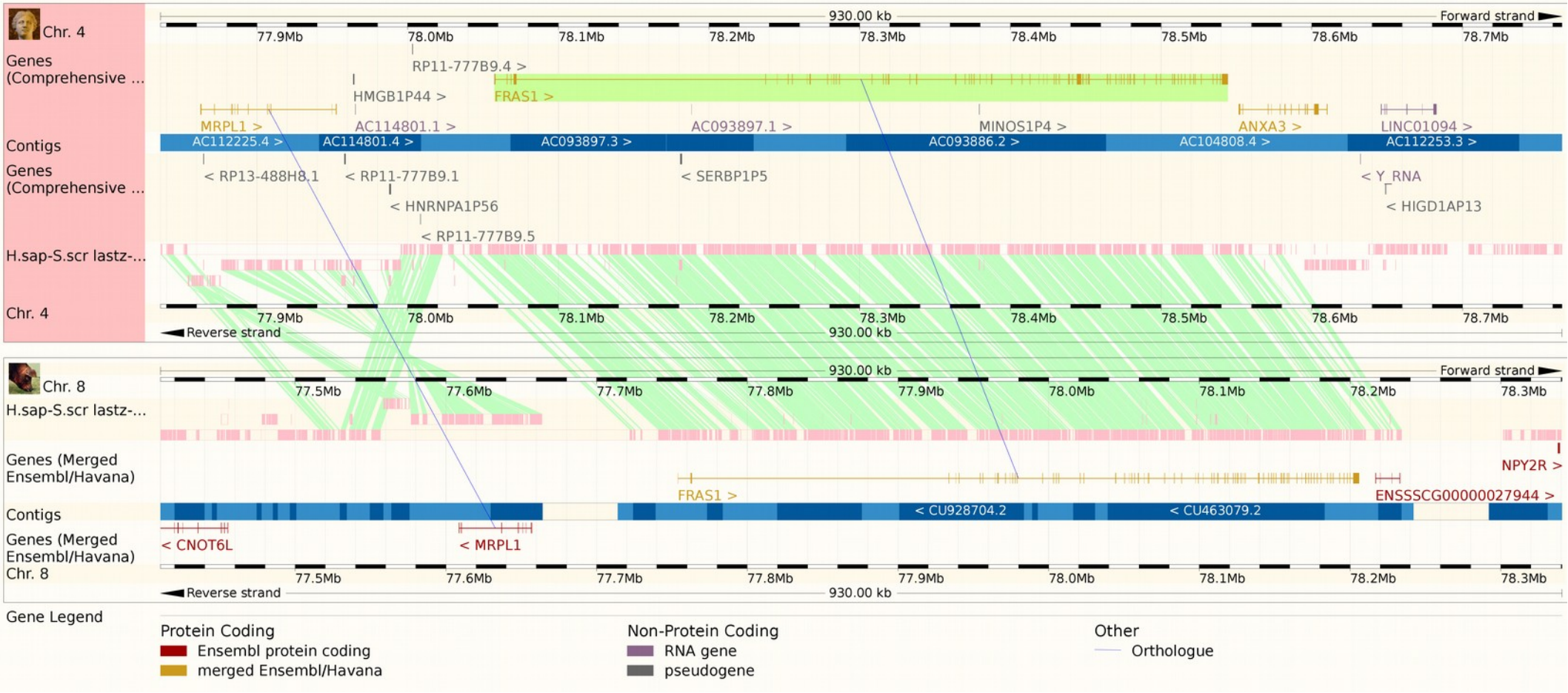
Outline of the course

- Introduction about Compara
  - Resources
  - API
- Inputs
  - Species, Chromosomes, Genes
- Outputs
  - Gene analyses
  - Genome analyses

Whole-genome alignments

Alignments at the DNA level

Example: Human vs pig



How are alignments stored ?

A small example :

```
gorilla_gorilla/MT/935-953    gacat-ttaactaaaac-ccc
macaca_mulatta/MT/1469-1488   aacatcttaactaaacg-ccc
pan_troglodytes/MT/934-953    gatac-ttaacttaaaccccc
pongo_pygmaeus/MT/940-958     actac-ctaactaaaac-ccc
homo_sapiens/MT/1516-1534     gacat-ttaactaaaac-ccc
                                 *    *****  **    ***
```

```
GACATTTAACTAAAACCCC       5MD11MD3M
AACATCTTAACTAAACGCCC      17MD3M
GATACTTAACTTAAACCCCC      5MD15M
ACTACCTAACTAAAACCCC       5MD11MD3M
GACATTTAACTAAAACCCC       5MD11MD3M
```

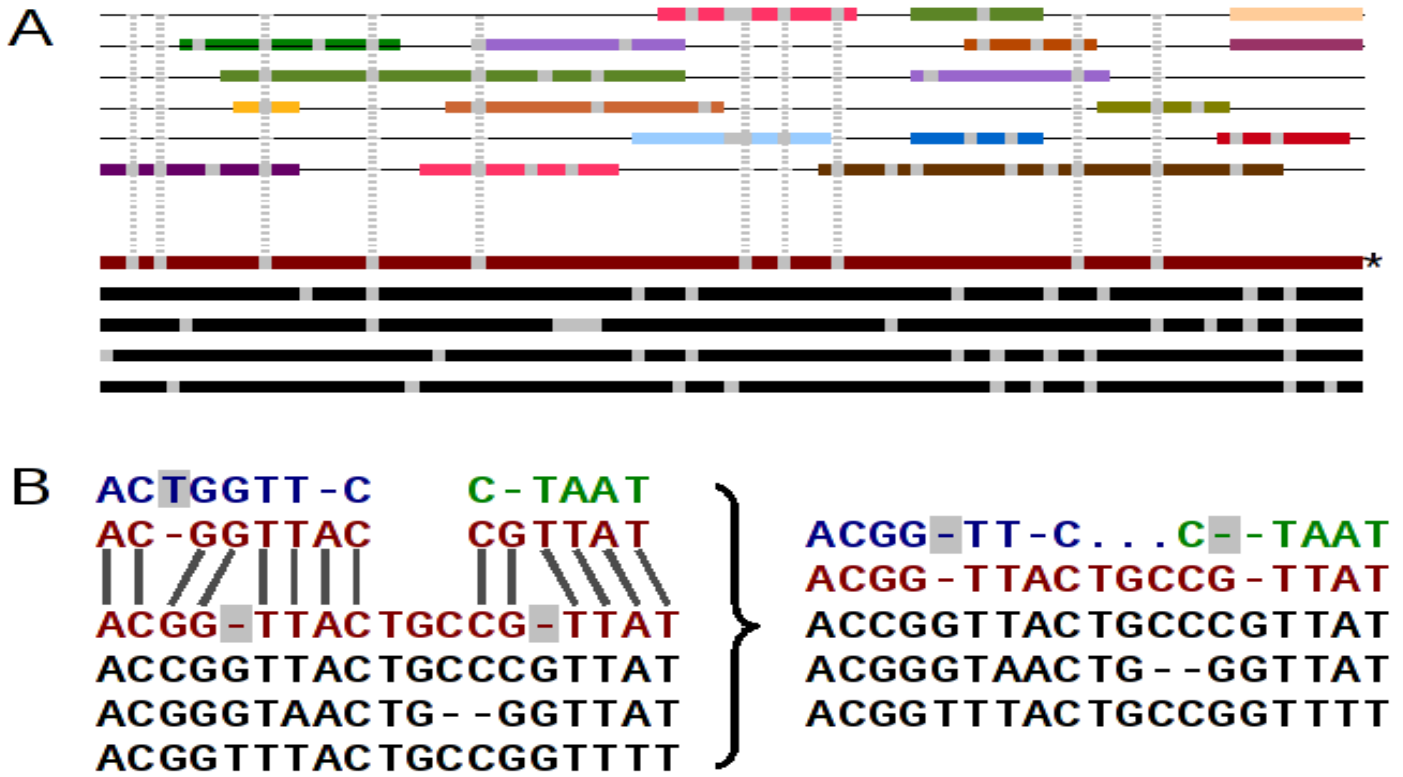
5 *genomic_align* entries
1 *genomic_align_block* entry

Sequences from core

CIGAR line in Compara

Adding low-coverage genomes

- Low coverage genomes cannot be fully assembled
- Resulting assembly is too scattered to be used with Enredo
- Run EPO on high-coverage genomes only
- Map 2X genomes using pairwise alignments on a reference species



Objects on the genomic side

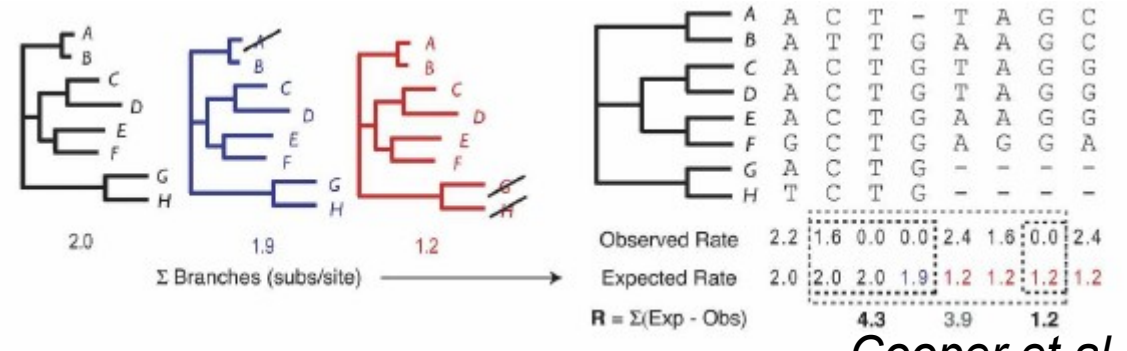
- A GenomicAlignBlock represents an alignment between two or more regions of genomic DNA. Within these blocks every region of genomic DNA is represented by a GenomicAlign object.

- A ConstrainedElement represent regions in the multiple alignment which appear to be under functional constraint.

- Synteny blocks are derived from Lastz-net alignments
  - group syntenic alignments closer than 200Kb
  - link syntenic groups closer than 3Mb
  - minimum length of the syntenic block: 100 kb

GERP Constrained Elements

- Stretches of the alignment with a high conservation



Cooper et al. Genome Research, 2005

- Constrained elements and coding exons
  - 74% of coding exons are associated with constr. elem.
  - 22% of constr. elem. are associated with coding exons

GenomicAlignBlock

- An alignment-block (across 2 or more sequences)
- The adaptor returns the blocks that **overlap** the query region
  → Call restrict_between_reference_positions()

Attributes	Methods
BioPerl alignment object	*$gab->get_SimpleAlign()*
Aligned sequences	*$gab->get_all_GenomicAligns()*
(Restrict the block)	*$gab->restrict_between_reference_positions()*
Adaptor methods	
`$gab_adaptor->fetch_all_by_MethodLinkSpeciesSet_Slice()`	

- GenomicAlign has a similar interface to Members, e.g. $ga→dnafrag, $ga→dnafrag_start, etc

Code Example - GenomicAlignBlock

```
my $mlss_adaptor = $reg->get_adaptor("Multi", "compara", "MethodLinkSpeciesSet");
my $genomic_align_block_adaptor = $reg->get_adaptor("Multi", "compara",
"GenomicAlignBlock");

my $epo_mlss_list = $mlss_adaptor->fetch_all_by_method_link_type("EPO");

foreach my $epo_mlss ( @{ $epo_mlss_list } ){
   my $genomic_align_blocks = $genomic_align_block_adaptor->
                                    fetch_all_by_MethodLinkSpeciesSet( $epo_mlss );
   print $epo_mlss->name() . " has " . scalar( @{ $genomic_align_blocks } ) .
            " alignment blocks\n";
}
```

Exercises – Genomic Alignments

- Print the LASTZ-NET alignments for pig chromosome 15 with cow (using pig coordinates 105734307 and 105739335).

- Change the above example so that it prints the 17-way eutherian mammal (EPO) multiple alignments.

- Print the constrained element alignments from the above pig locus (use the constrained elements generated from the EPO_LOW_COVERAGE mammals alignments)

Exercises – Synteny

- Print the pig-cow synteny map using pig chromosome 15 as a reference

  web reference:
  http://www.ensembl.org/Sus_scrofa/Location/Synteny?r=15&otherspecies=Bos_taurus

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