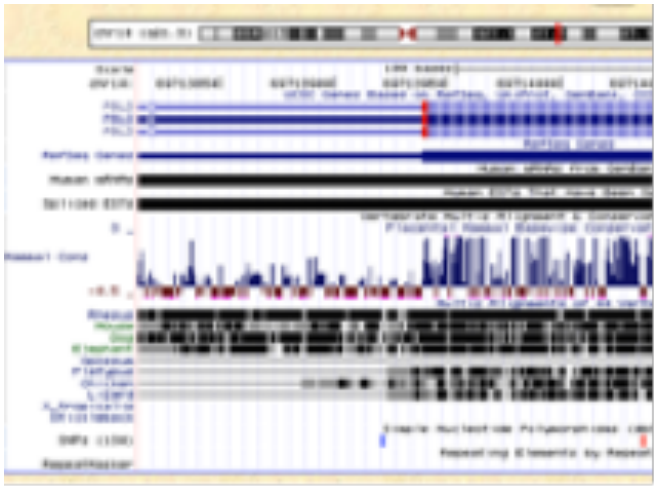
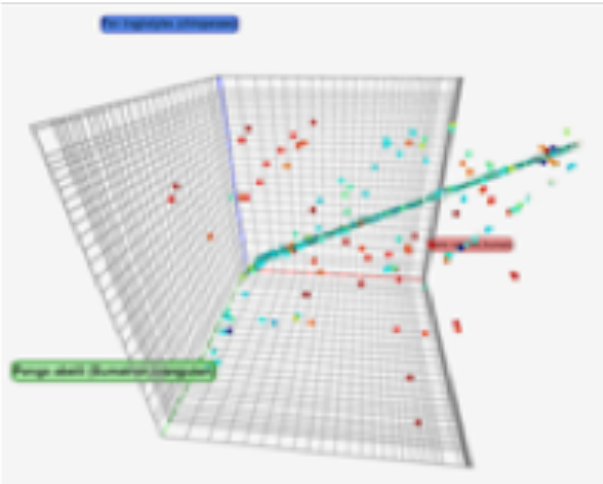
Computational Genomics

Introduction
to
Gene Models and Gene Tables





Fasta Format

A sequence in FASTA format begins with a single-line description, followed by lines of sequence data. The description line (defline) is distinguished from the sequence data by a greater-than (">") symbol at the beginning. It is recommended that all lines of text be shorter than 80 characters in length. An example sequence in FASTA format is:

```
>P01013 GENE X PROTEIN (OVALBUMIN-RELATED)
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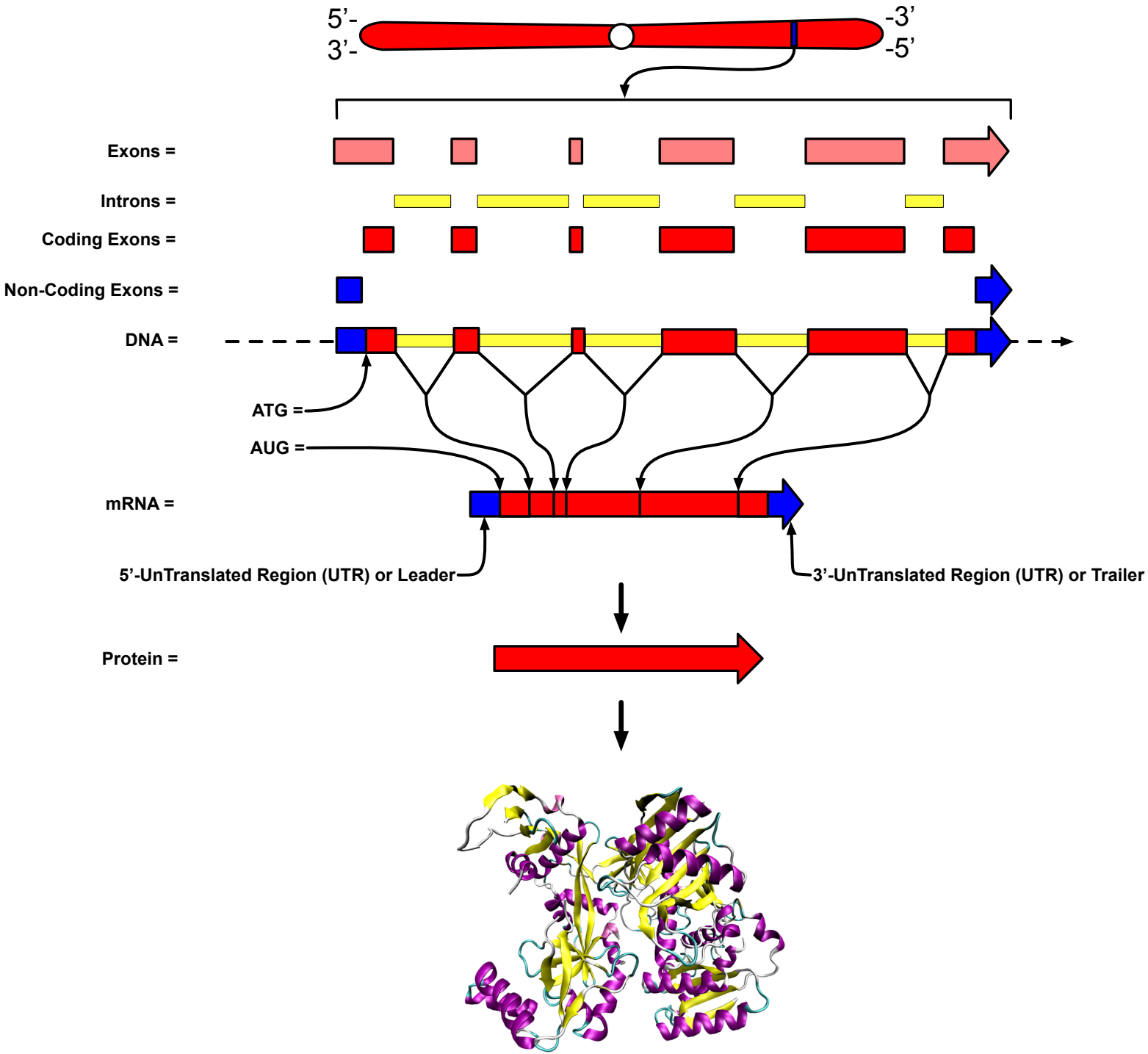
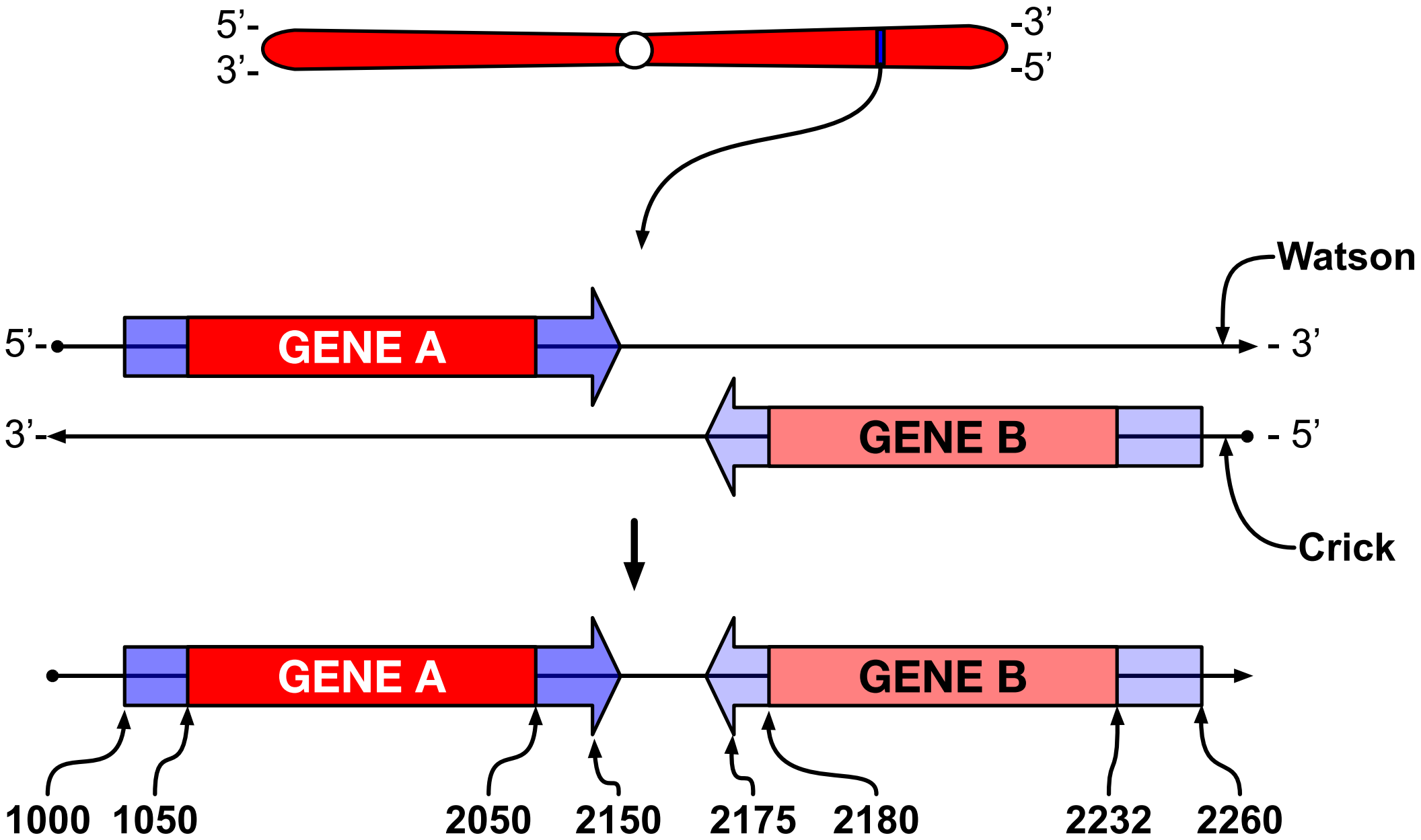
Gene Models 101

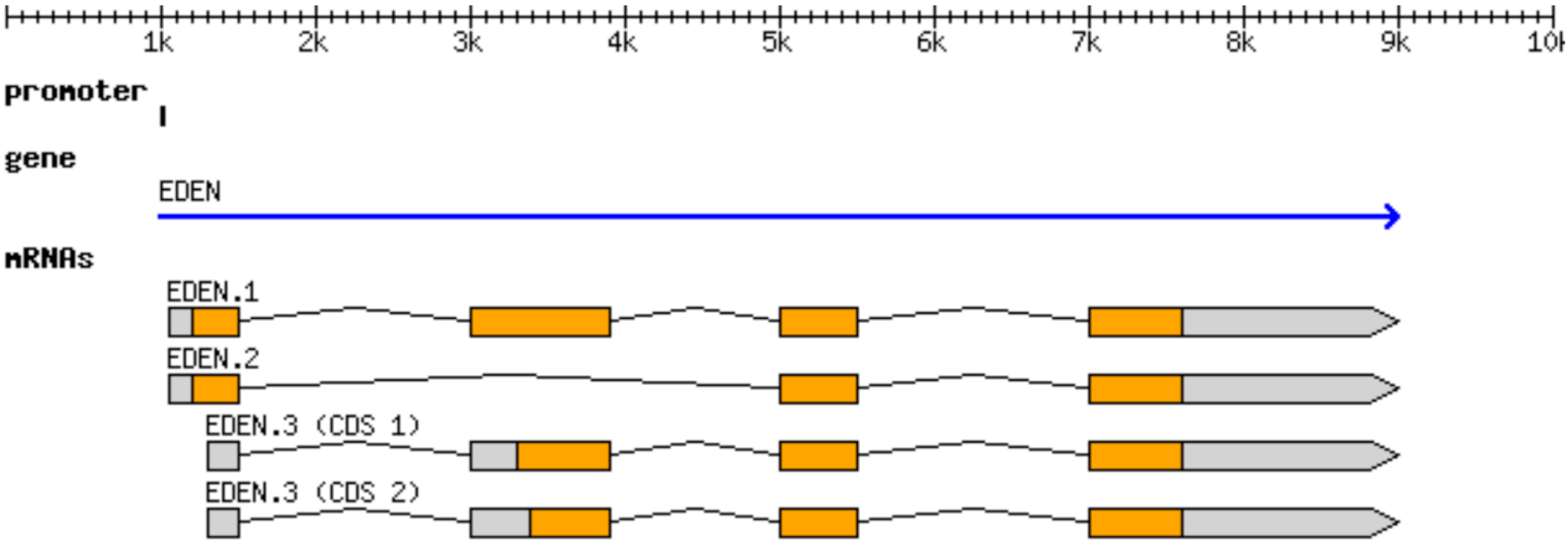


Gene Tables 101



GFF File Format and Gene Models

The Canonical Gene



https://github.com/The-Sequence-Ontology/Specifications/blob/master/gff3.md

GFF File Format and Gene Models

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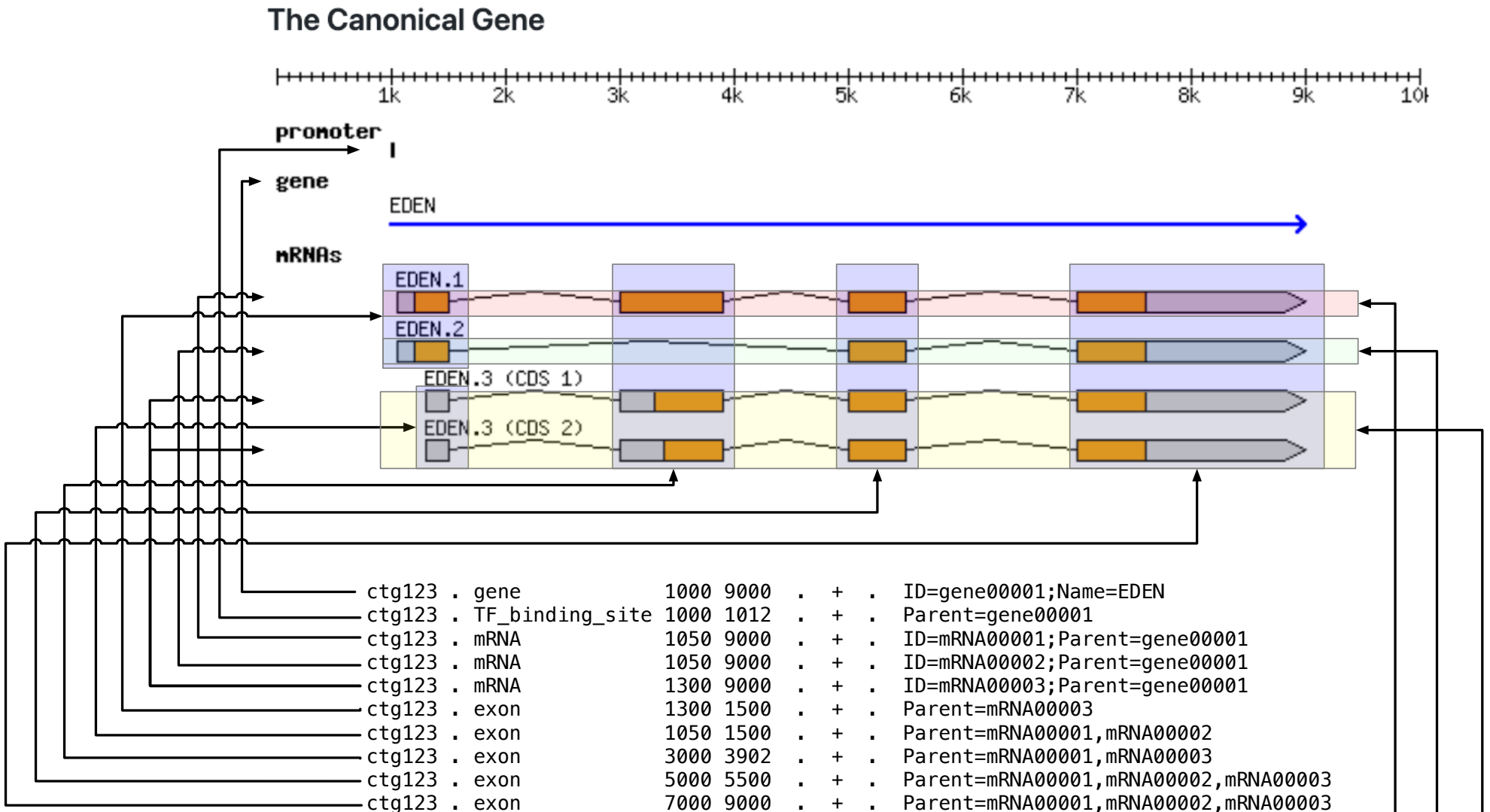
https://github.com/The-Sequence-Ontology/Specifications/blob/master/gff3.md

GFF File Format and Gene Models

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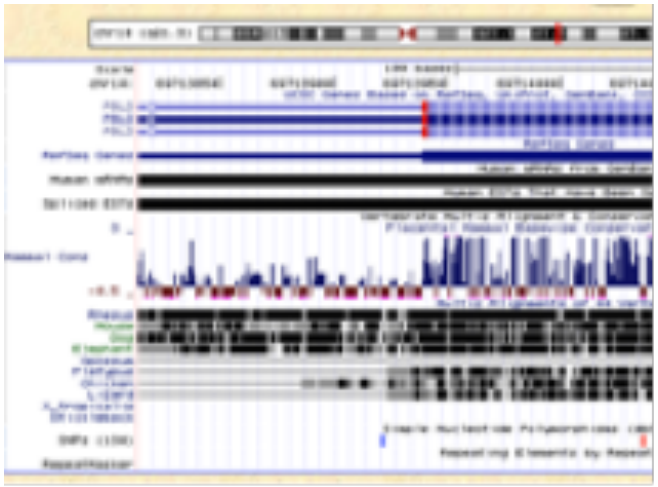
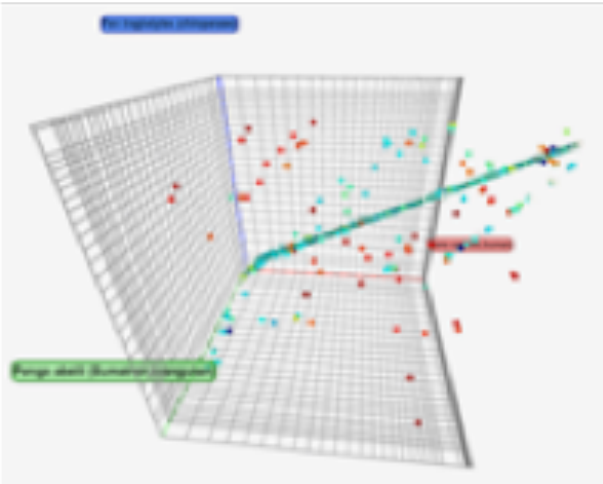
Computational Genomics

Introduction to Genome Browsers
ENSEMBL





Training materials

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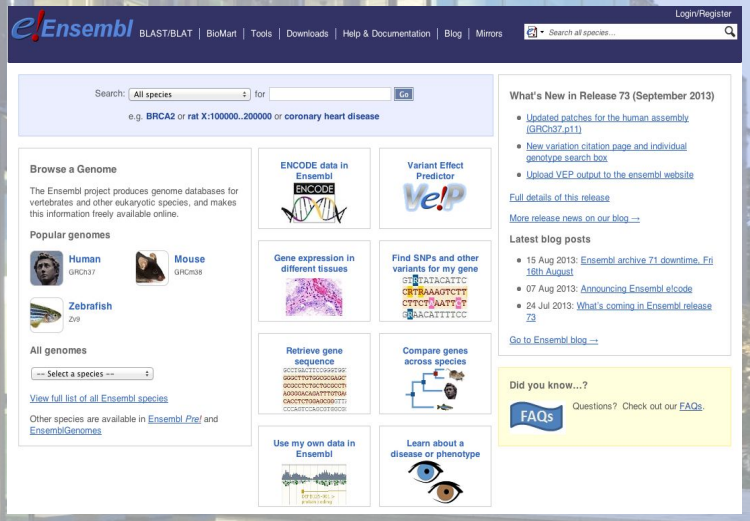
- If you use Ensembl for your work, please cite our papers:

  ensembl.org/info/about/publications.html

Exploring the Ensembl genome browser



EMBL-EBI

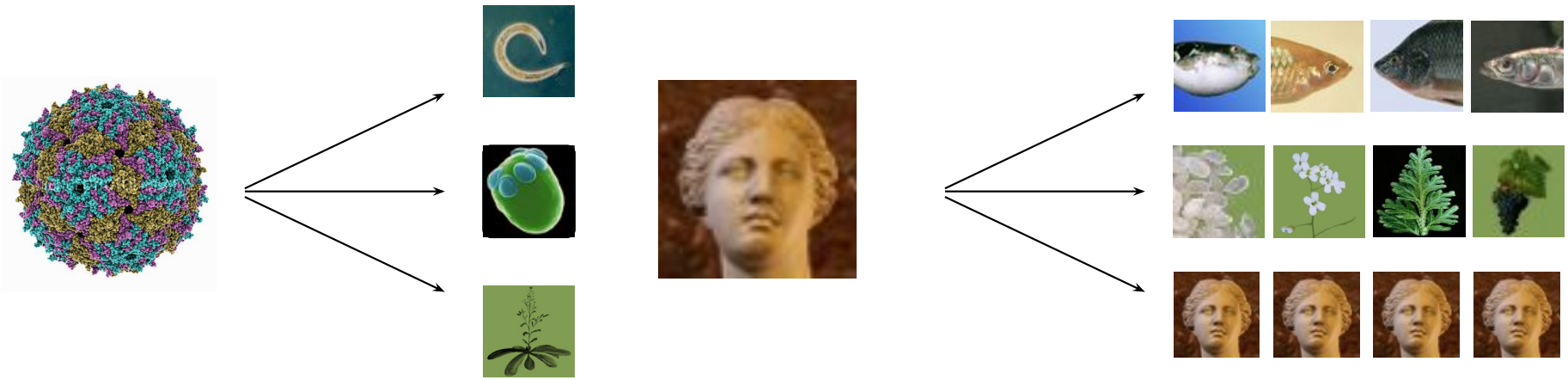
Ensembl

Introduction

Why do we need genome browsers?

1977: 1st genome to be sequenced (5 kb)

2004: finished human sequence (3 Gb)



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What is Ensembl?

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Ensembl annotates and maps genomic features from genome sequences

What is Ensembl?

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Ensembl is an ‘added value resource’ bringing together information from a wide range of other databases in a single site

What is Ensembl?

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NIH U.S. National Library of Medicine | NCBI

Genome Data Viewer

www.ncbi.nlm.nih.gov/genome/gdv/

e!Ensembl

www.ensembl.org

UCSC

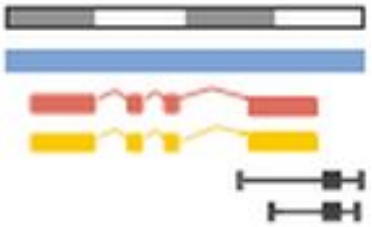
www.genome.ucsc.edu

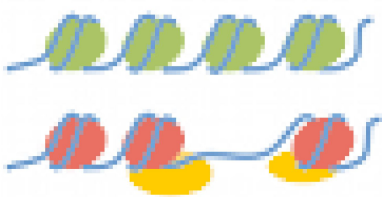
e!EnsemblGenomes

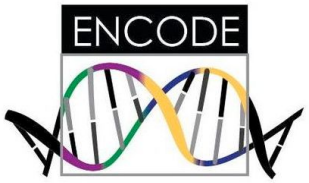
www.ensemblgenomes.org

Ensembl features

- Gene builds for >300 species
- Gene trees
- Regulatory build (ENCODE)
- Variation display and VEP
- Display of user data
- BioMart (data export)
- Programmatic access via the APIs
- Completely Open Source







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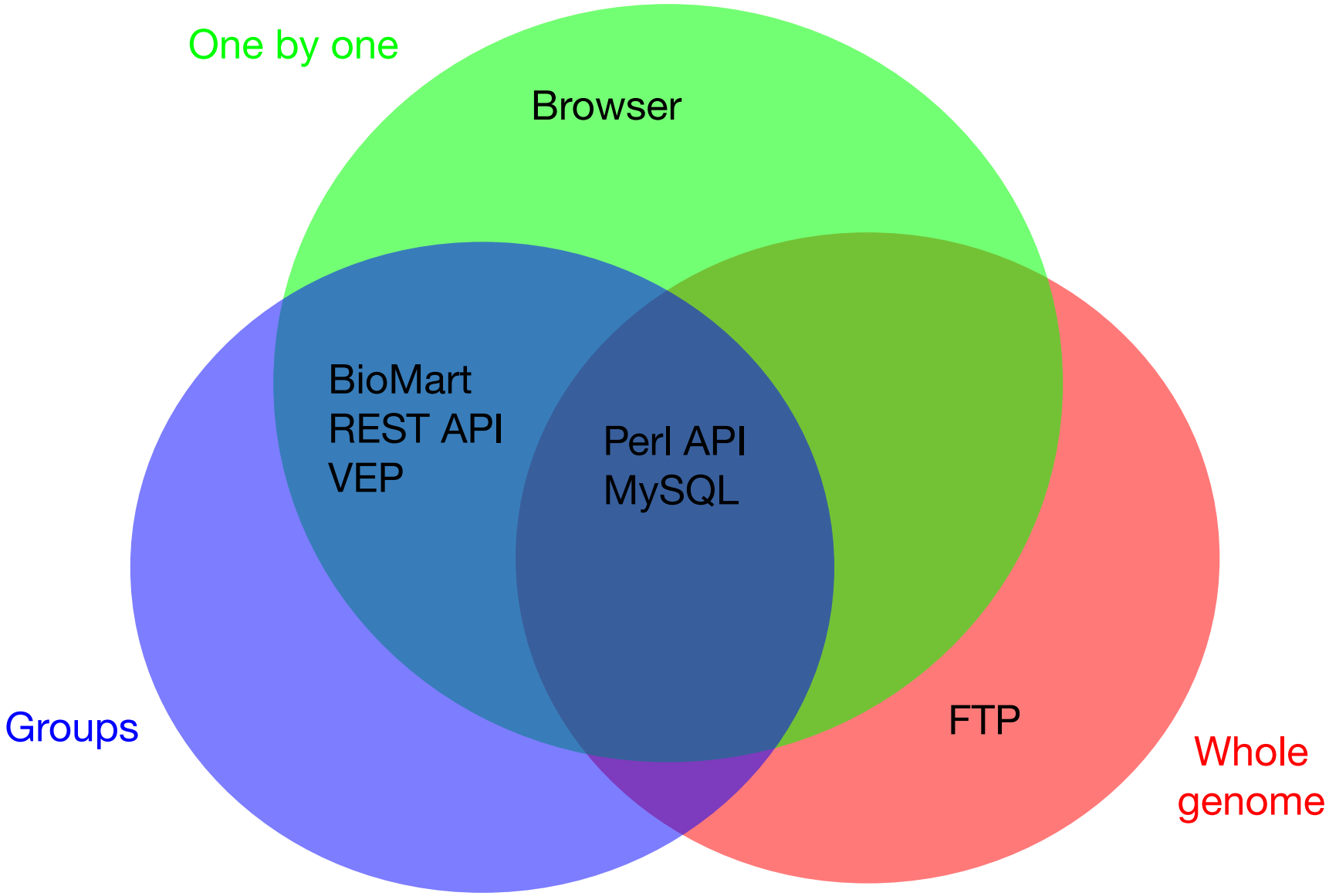
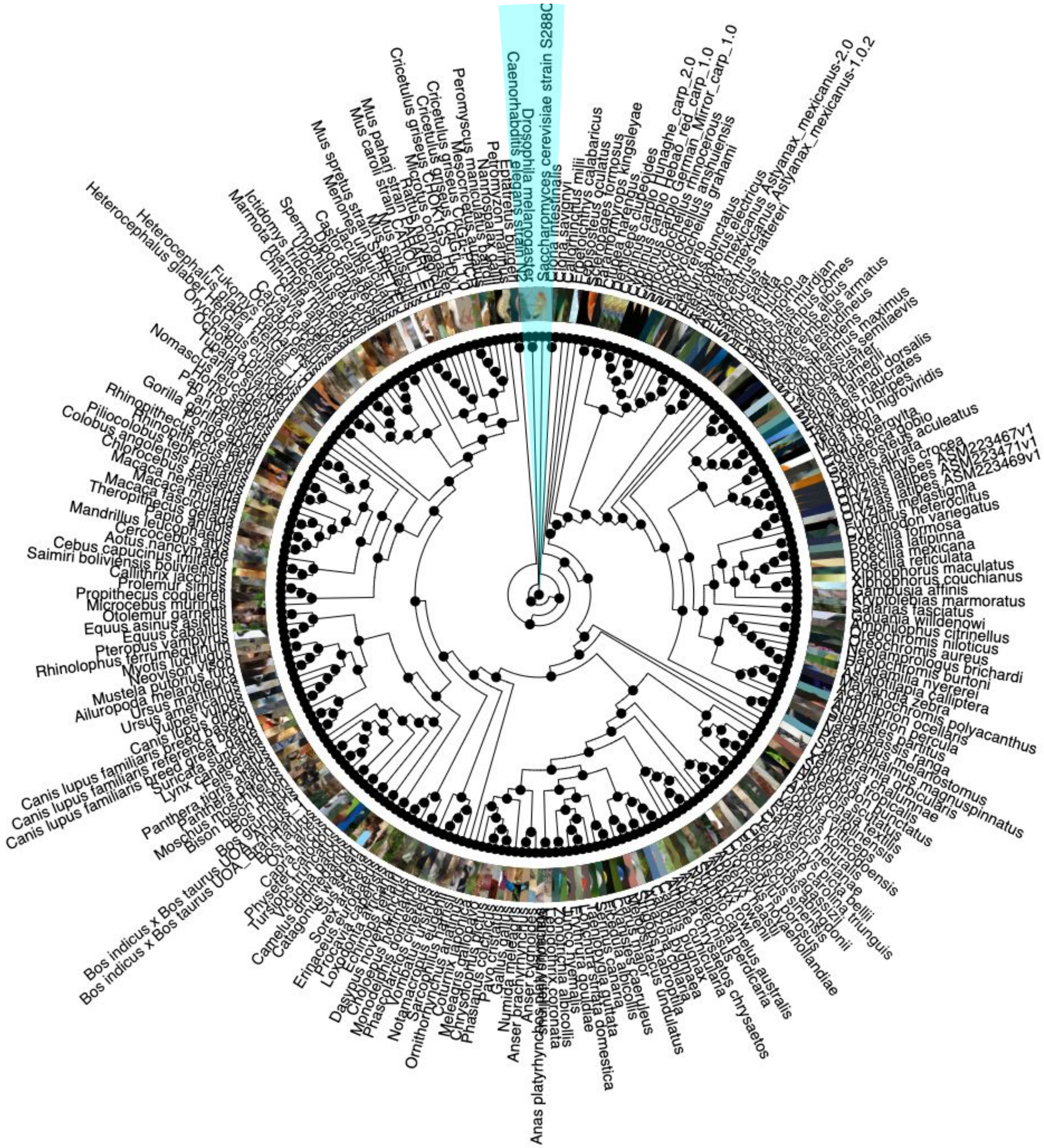
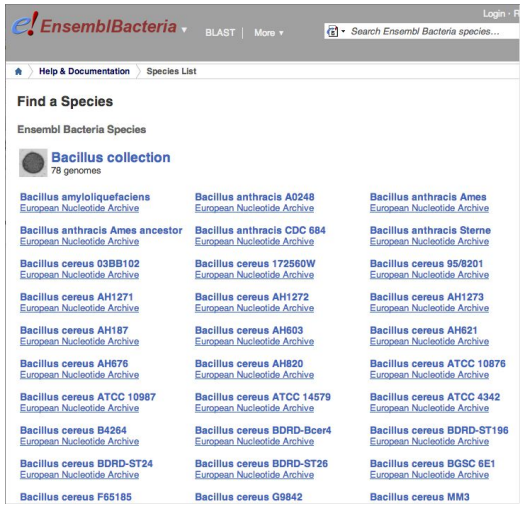


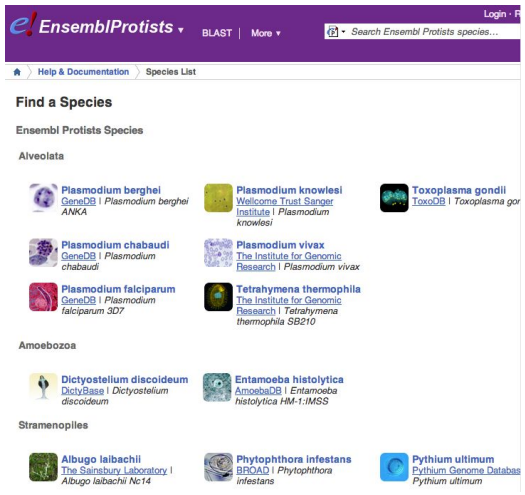
Vertebrate species in Ensembl



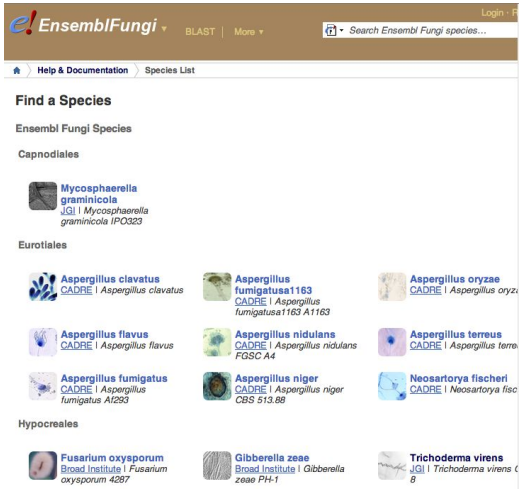
Non-vertebrates on Ensembl genomes



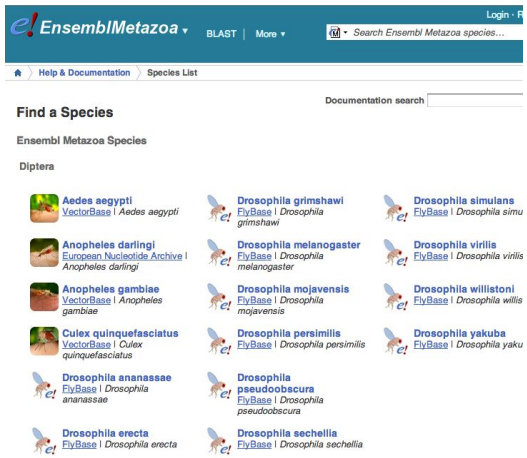
Bacteria



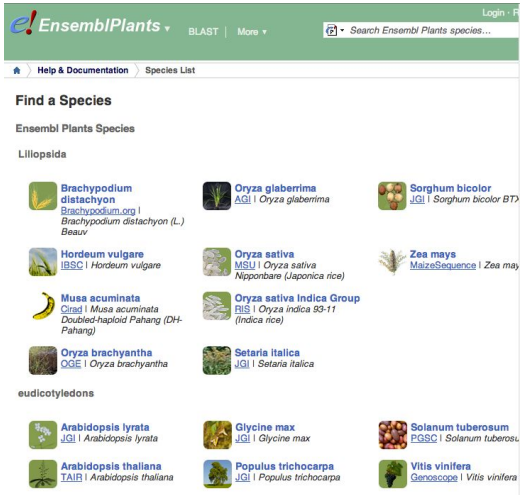
Protists



Fungi



Metazoa



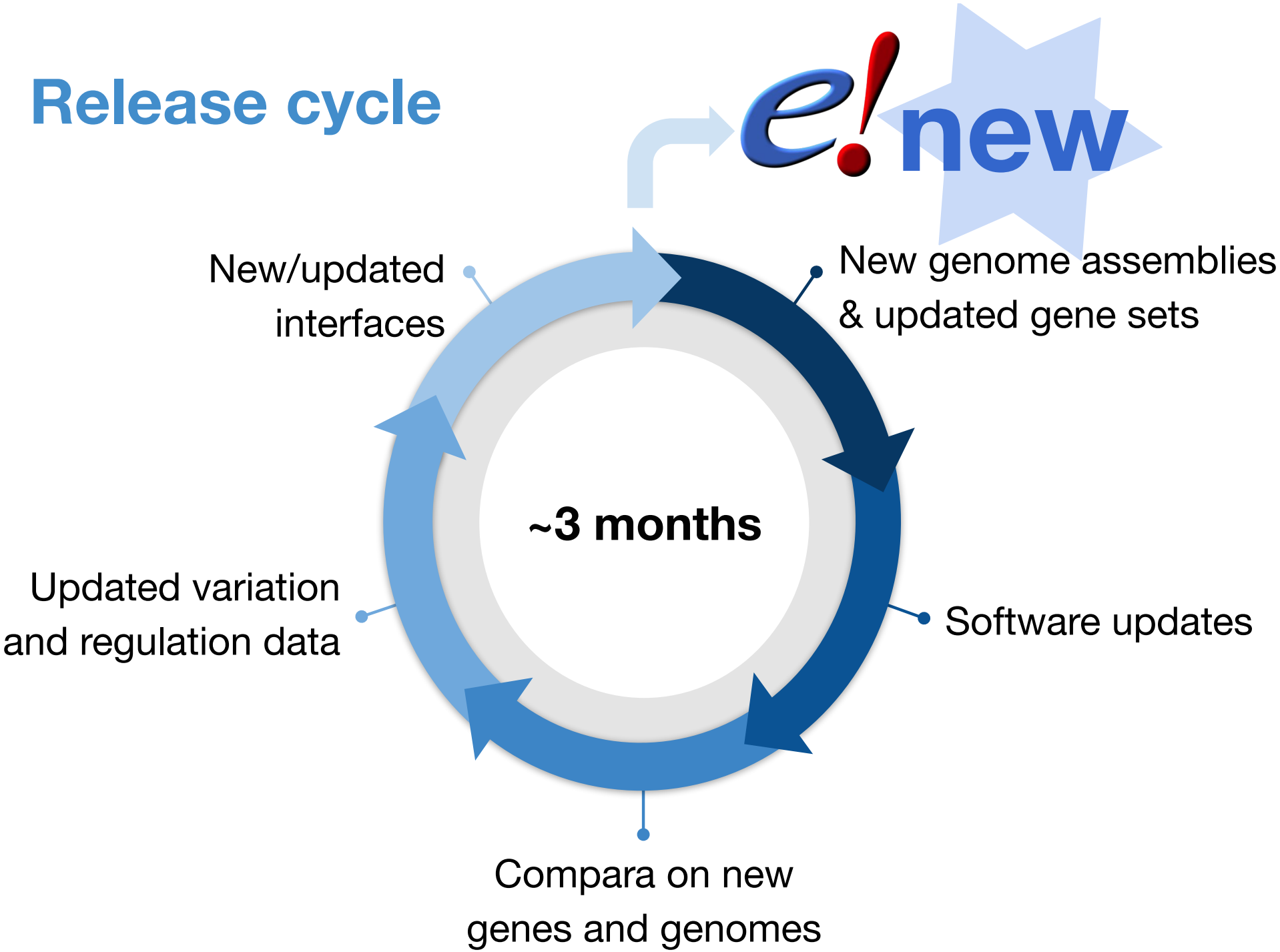
Plants

www.ensemblgenomes.org

Ensembl and Ensembl Genomes

	Ensembl	Ensembl Genomes
Released	2000	2009
Species	Vertebrates (fly, worm and yeast as outgroups)	Non-vertebrates (protists, plants, fungi, metazoa, bacteria)
Annotation	by Ensembl	in collaboration with the scientific communities
URL	www.ensembl.org	www.ensemblgenomes.org

Release cycle



Ensembl Rapid Release

- Released every two weeks ✅
- Genome with gene annotation only ✅
- BLAST ✅
- No BioMart ❌
- No gene trees/homologues ❌
- No variation ❌

Cloning into BACs

BL

Cut into chunks and clone into BACs

Grow up in bacterial cultures

Making a contig

Sequence reads

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                    CAGATGACGCC
```

Match up overlaps

```
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       GGGCTCCGCCTTCAGCTC   ACTTAACTTCCCTCCCAGCTGTCC
CGGCCTTTGGGCTCC                          CAGCTGTCCCAGATGAC
```

Contig

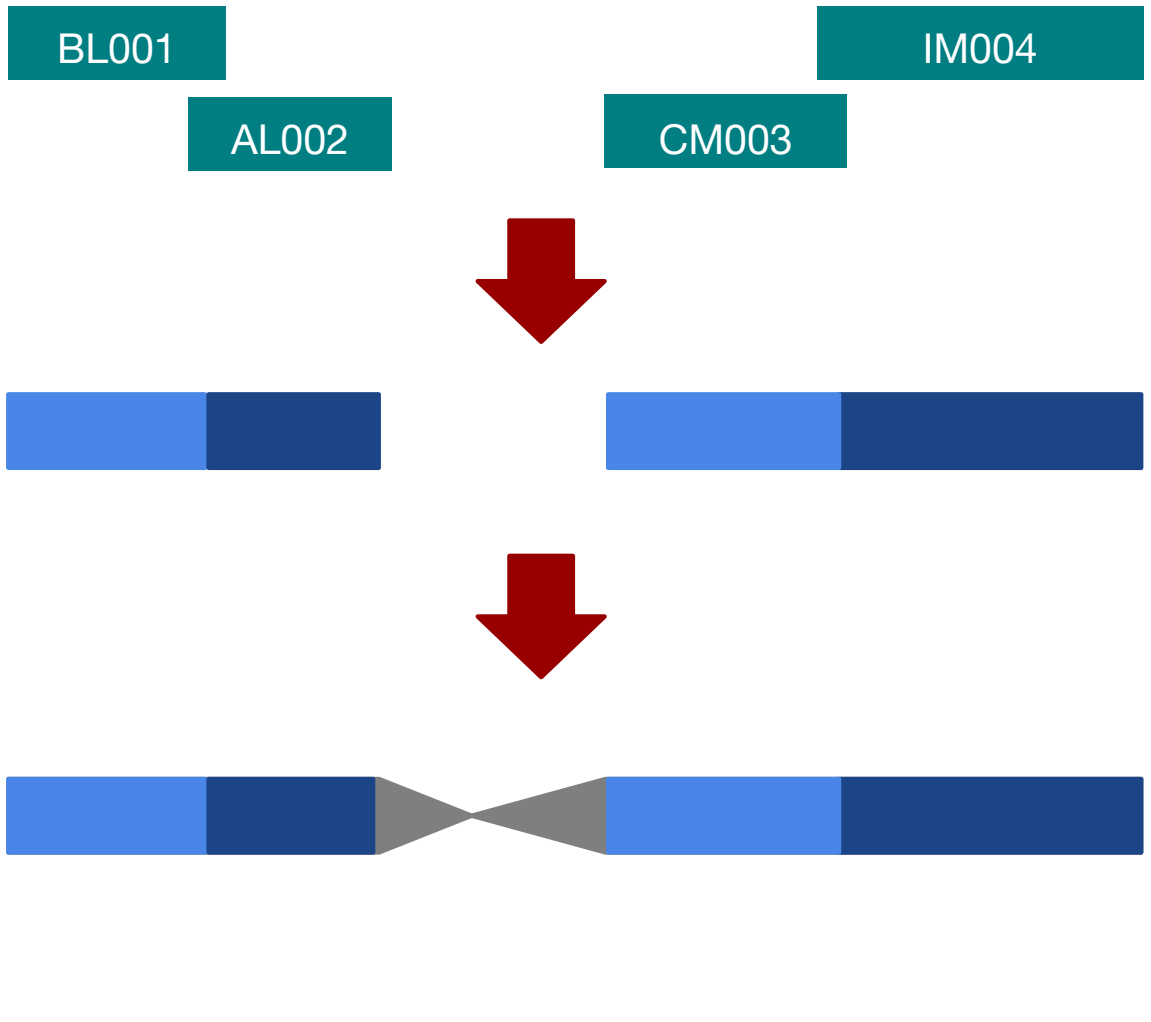
```
CGGCCTTTGGGCTCCGCCTTCAGCTCAAGACTTAACTTCCCTCCCAGCTGTCCCAGATGACGCCATC
```

Contigs to scaffolds

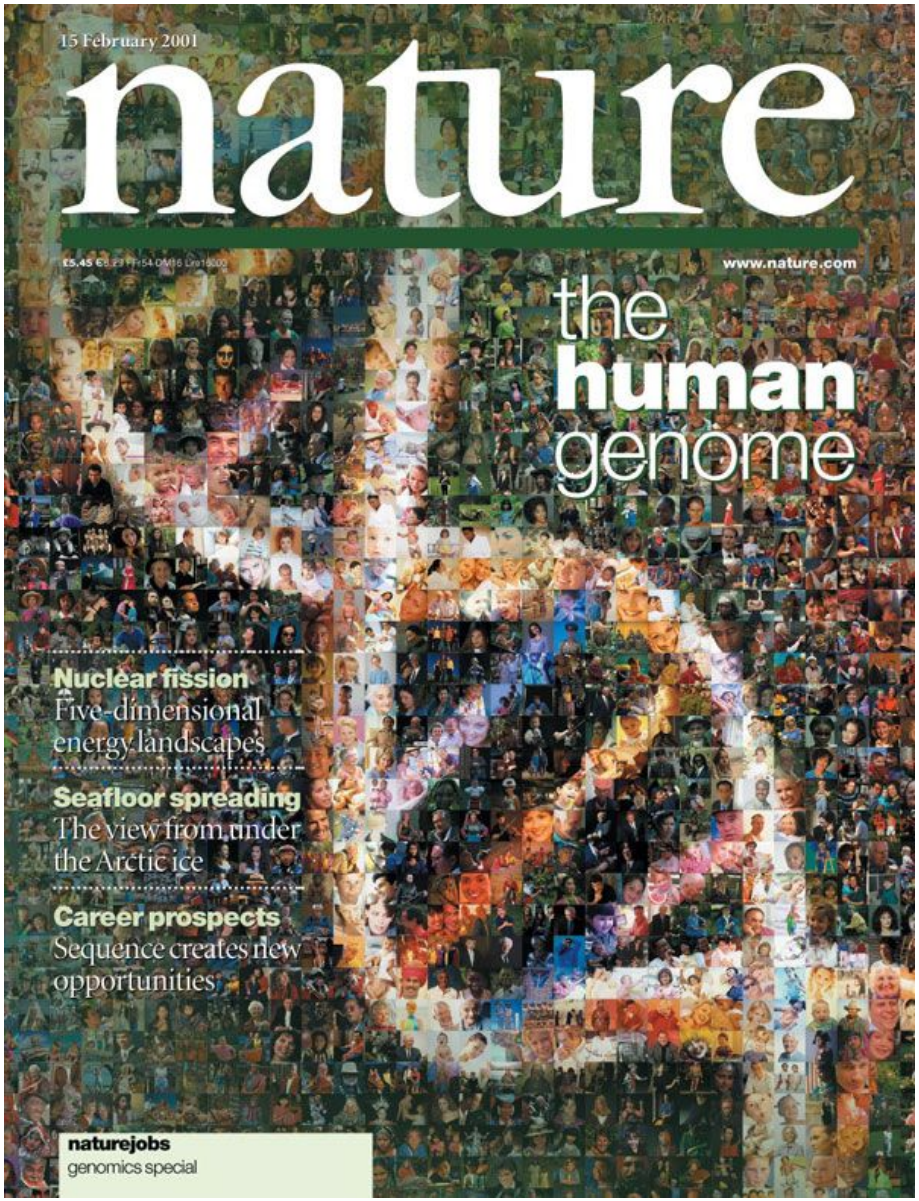
BACs from different individuals assembled together with overlaps Tilepath

Overlaps trimmed to give contigs. A run of contigs with no gaps is a scaffold.

Genetic maps are used to assemble scaffolds into a chromosome



Genome assemblies



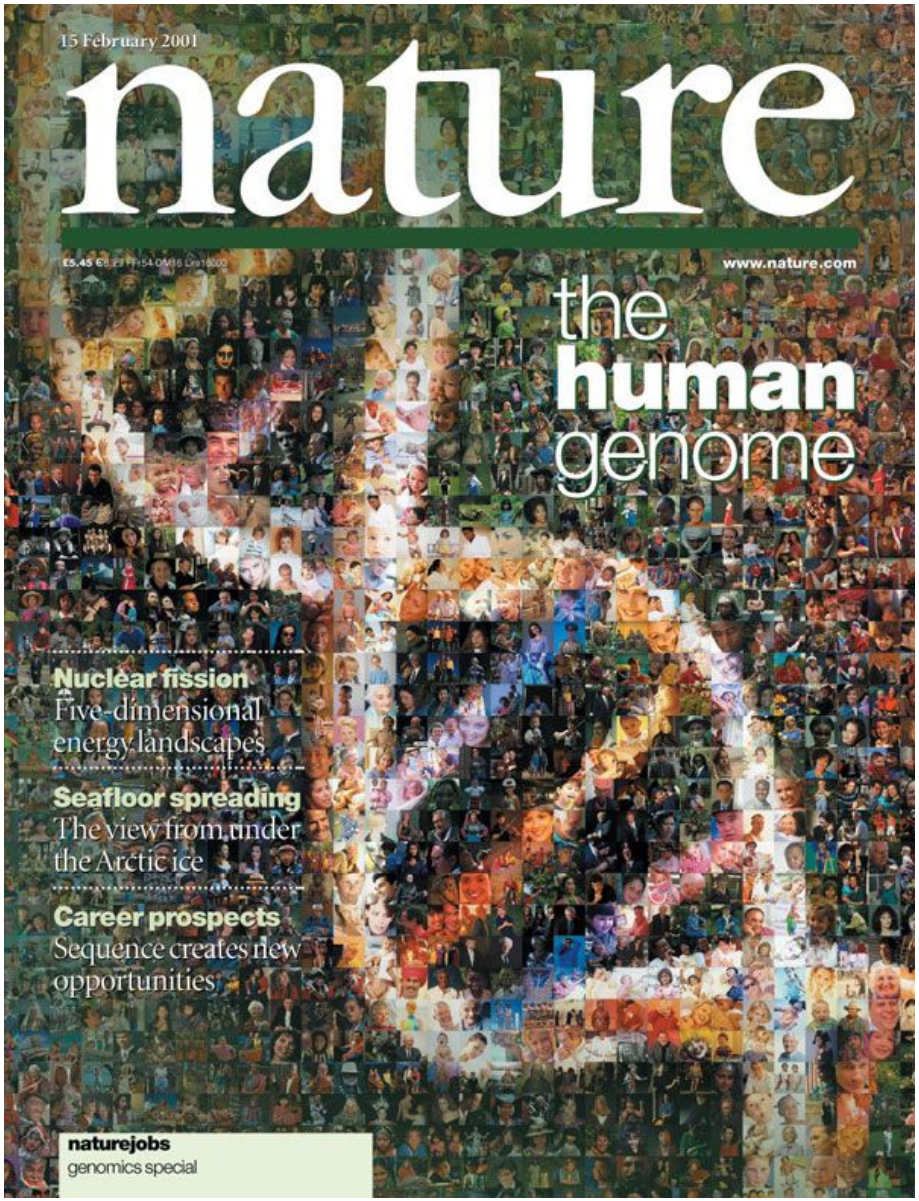
BL

AL

CM

IM

Genome contigs



BL

AL

CM

IM

BL001
AL002
CM003
IM004

Genome assemblies

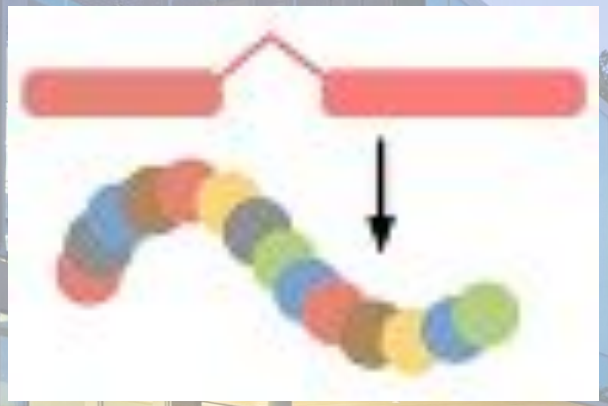
Genome
"DNA within a cell"

Genome *assembly*
Representation of a genome
Contains errors and gaps
Coordinate system

Human genome assemblies

- GRCh38 (aka hg38) 
  - Many rare/private alleles replaced.
  - www.ensembl.org
  - Most up-to-date and supported
- GRCh37 (aka hg19) 
  - Some large gaps
  - grch37.ensembl.org
  - Limited data and software updates
  - Still the preferred genome of the clinical community
- NCBI36 (aka hg18) 
  - Many gaps
  - ncbi36.ensembl.org
  - No longer updated

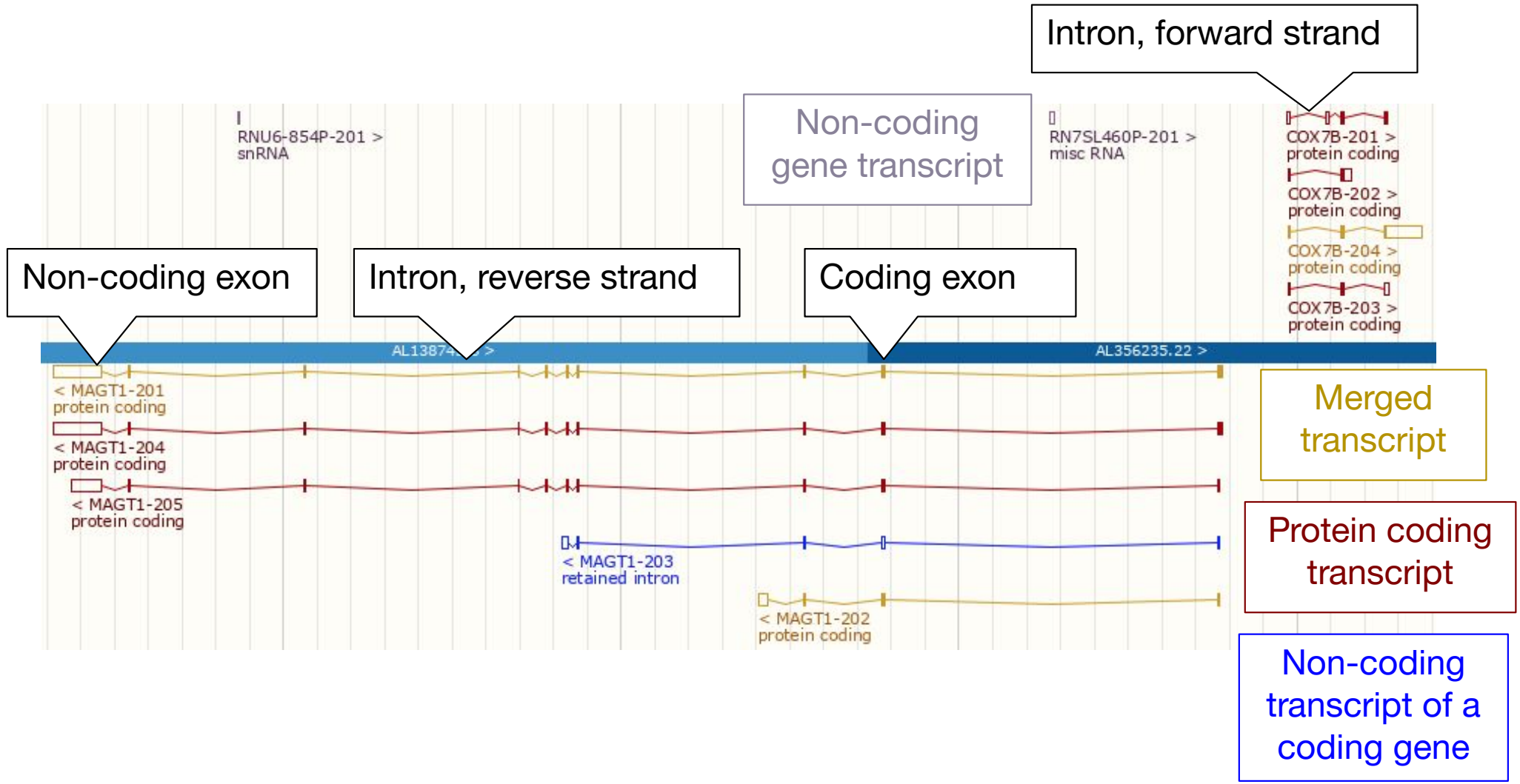
Genes and Transcripts



EMBL-EBI

Ensembl

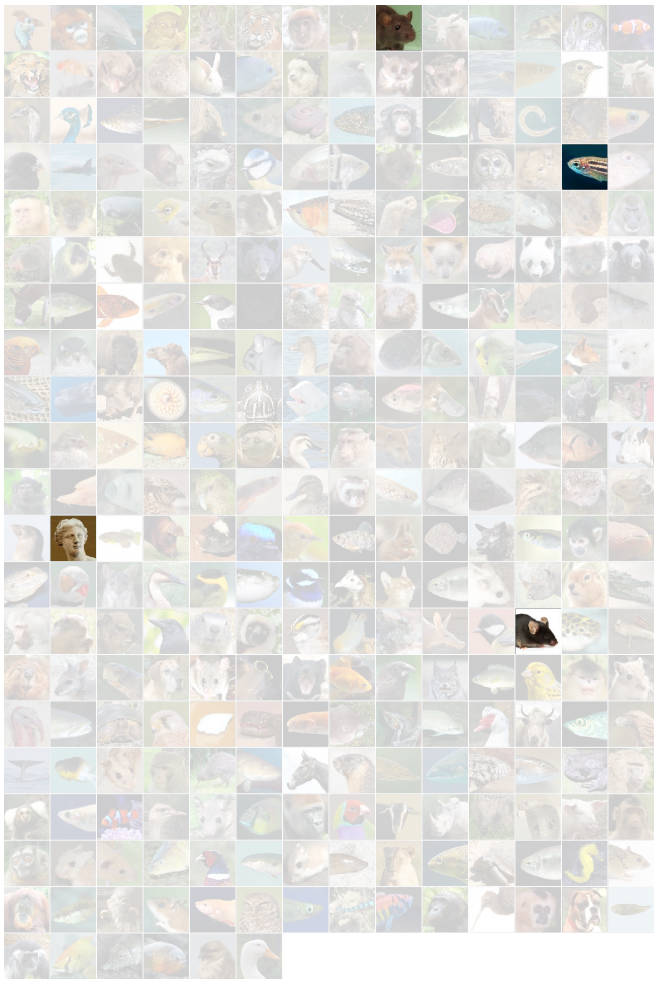
Gene views


Intron, forward strand
Non-coding gene transcript
RNU6-854P-201 >
snRNA
RN7SL460P-201 >
misc RNA
COX7B-201 >
protein coding
COX7B-202 >
protein coding
COX7B-204 >
protein coding
COX7B-203 >
protein coding
Non-coding exon
Intron, reverse strand
Coding exon
AL356235.22 >
< MAGT1-201
protein coding
< MAGT1-204
protein coding
< MAGT1-205
protein coding
< MAGT1-203
retained intron
< MAGT1-202
protein coding
Merged transcript
Protein coding transcript
Non-coding transcript of a coding gene

Automatic and manual annotation

Automatic annotation

Manual annotation



Automatic and manual annotation

Automatic annotation

- computational pipeline
- one genone = two weeks

Manual annotation

- human annotator
- one genome = several years

Annotation sources

Automatic annotation

- INSDC
  - cDNAs
  - ESTs
  - RNA-seq
- Protein sequence databases
  - Swiss-Prot: manually curated
  - TrEMBL: unreviewed translations

Manual annotation

- RNA-seq transcriptome data
  - Illumina short read
  - Oxford Nanopore long read
  - PacBio long read
- Transcript structure data
  - Introns
  - CAGE transcription start sites
  - PolyA-Seq transcription ends
- Mass Spec protein data
- publications

Manual vs automatic

- Manual annotation is more comprehensive
  - More transcripts per gene, especially non-coding transcripts
  - More genes overall, especially non-coding genes
- More biotypes
  - e.g. polymorphic pseudogene, NMD, non-stop decay, stop codon read-through
- Manual annotation can be more accurate for difficult to annotate features such as:
  - UTRs
  - Splice sites
  - Single exon transcripts
  - Exceptions, such as immunoglobulins, stop codon readthroughs

GENCODE == Ensembl human and mouse genes

GENCODE is the default gene set used by major projects such as:

- gnomAD/ ExAC: Exome Aggregation Consortium, Genome Aggregation
- GTEx: Genotype-Tissue Expression
- Decipher
- 100,000 Genomes Project, Genomics England
- ENCODE: Encyclopedia of DNA Elements
- TCGA: The Cancer Genome Atlas
- ICGC: International Cancer Genome Consortium
- Roadmap: NIH Roadmap Epigenomics Mapping Consortium
- Blueprint: Blueprint Epigenome
- 1000 Genomes Project
- HCA: Human Cell Atlas

Golden transcripts

- Identical annotation

- Higher confidence and quality

Ensembl stable IDs

- ENSG##########.# Ensembl Gene ID
- ENST##########.# Ensembl Transcript ID
- ENSP##########.# Ensembl Peptide ID
- ENSE##########.# Ensembl Exon ID

- For non-human species a suffix is added:

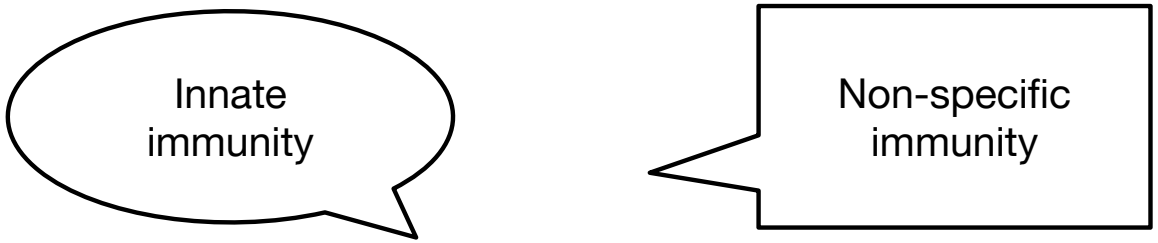
  MUS (*Mus musculus*) for mouse ENSMUSG###

  DAR (*Danio rerio*) for zebrafish: ENSDARG###

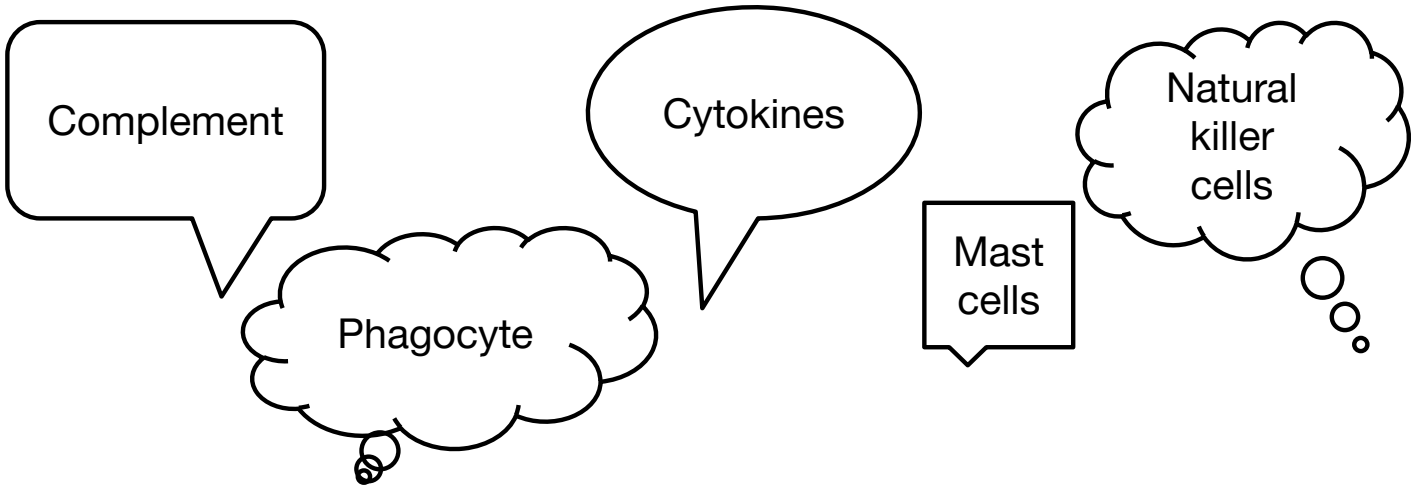
http://www.ensembl.org/info/genome/stable_ids/index.html

Why Gene Ontology (GO)?

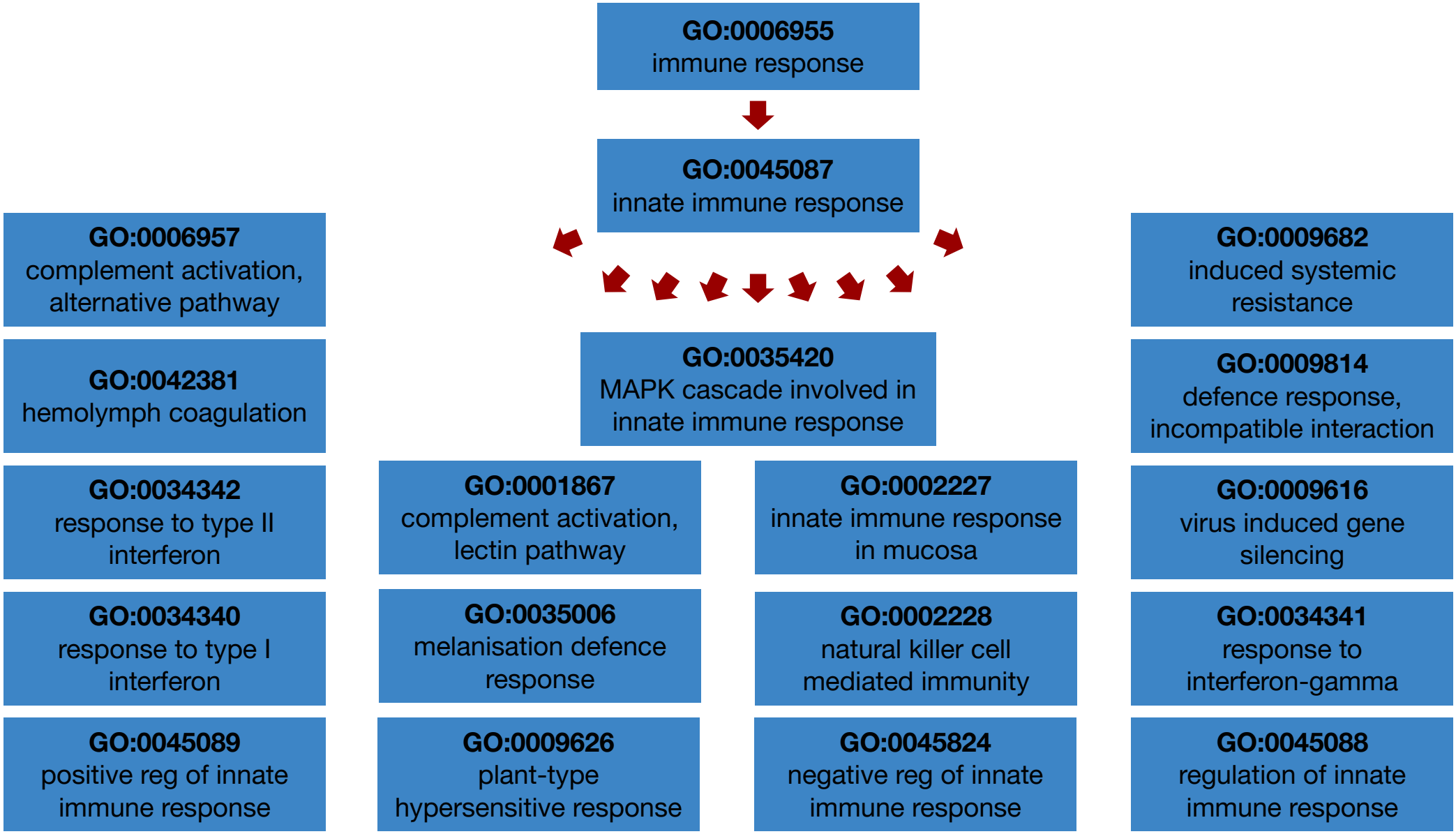
Multiple terms for the same thing



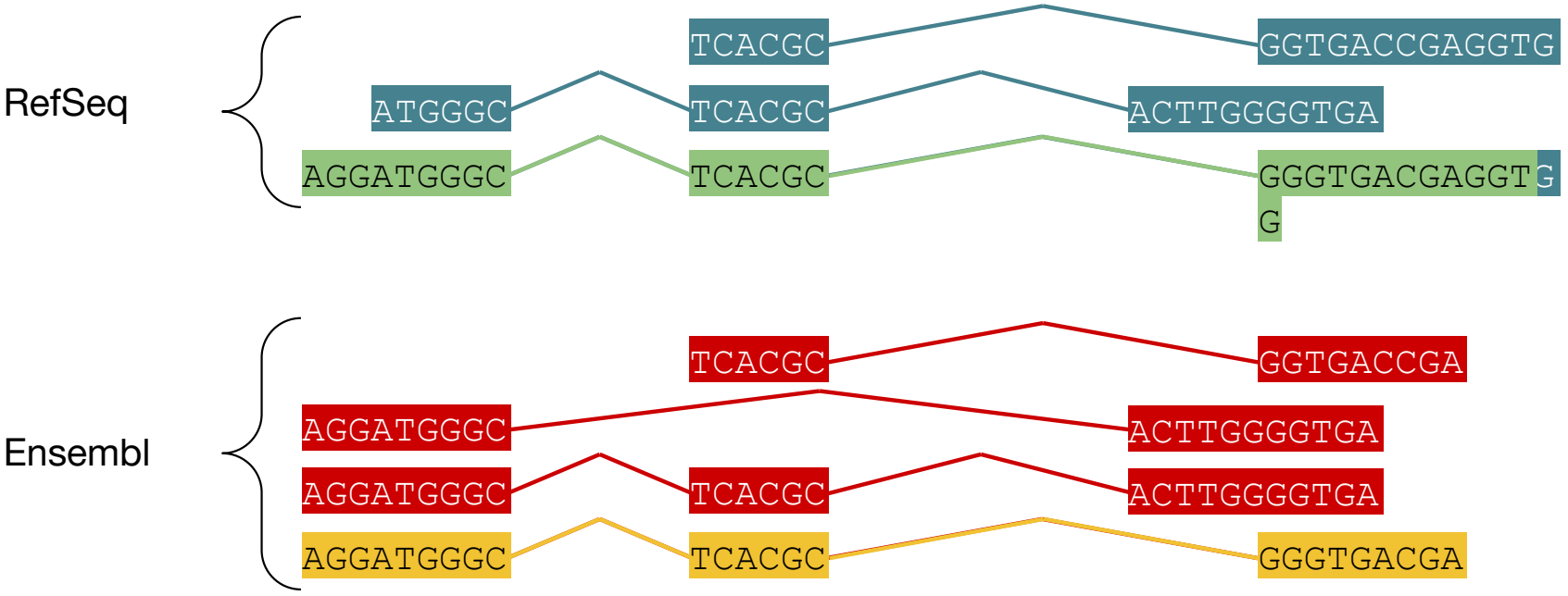
Gene descriptions too specific



GO terms are hierarchical



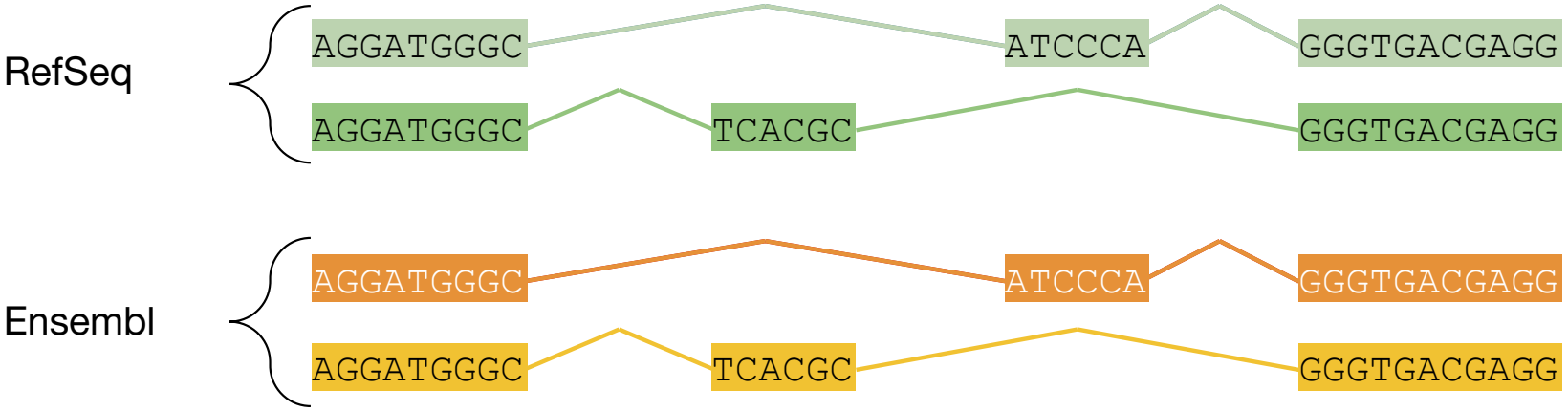
MANE Select



AACTAAGAATTTAAGGATGGGCGTGGTGGCTCACGCCTGTAATCCCAGCACTTGGGGTGACCGAGGTGGGCGGATCACTTGAGG

Select = most clinically relevant, based on expression levels, clinically important genetic variation and conservation between species

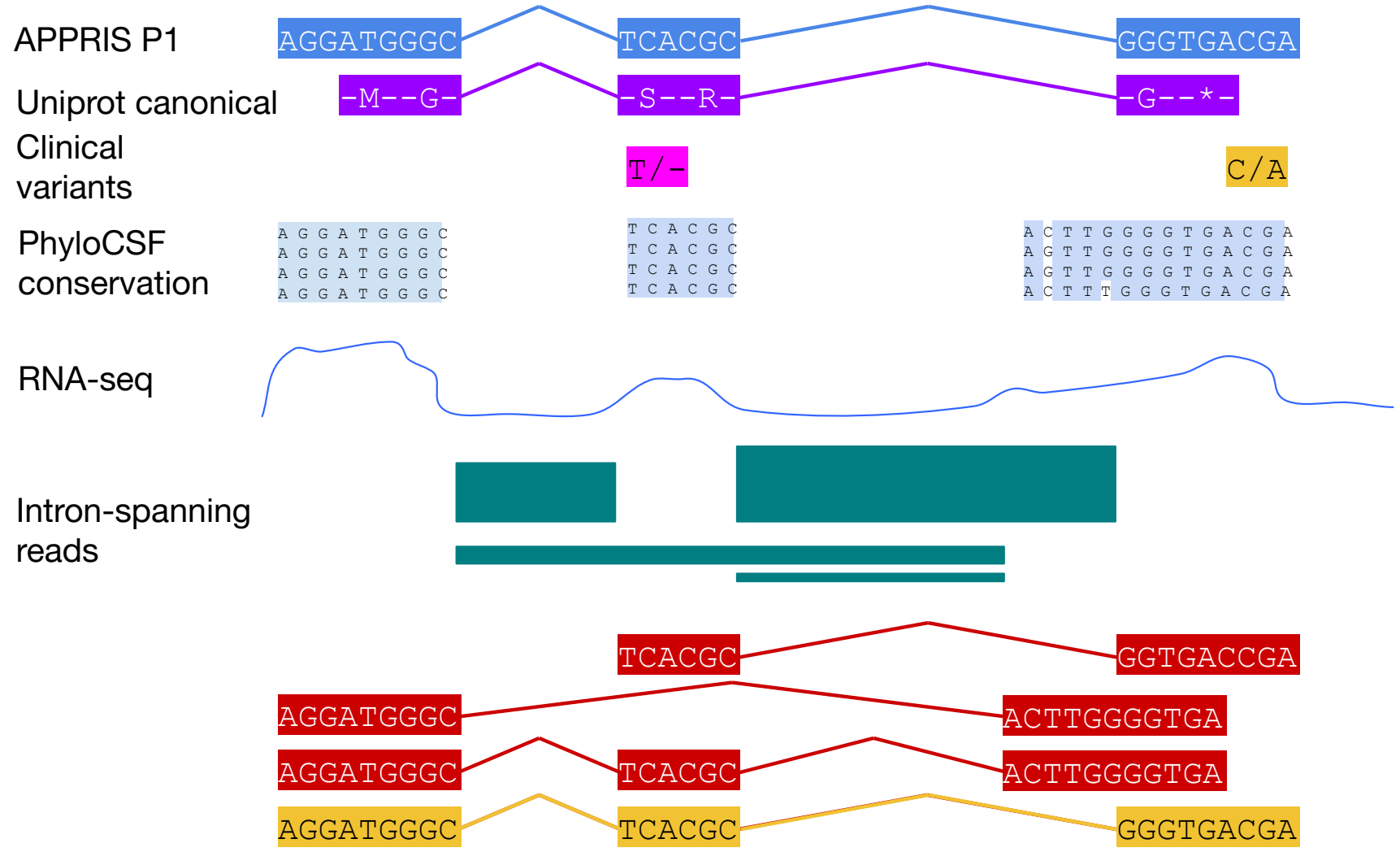
MANE Plus Clinical



AACTAAGAATTTAAGGATGGGCGTGGTGGCTC ACGCCTGTAATCCCA GCACTTGGGGTGACCGAGGTGGGCGGATCACTTGA
GG

Clinically important variants

Canonical transcript



AACTAAGAATTTAAGGATGGGCGTGGTGGCTCACGCCTGTAATCCCAGCACTTGGGGTGACCGAGGTGGGCGGATCACTTGA
GG