Package ‘AlphaMissenseR’

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Title Accessing AlphaMissense Data Resources in R

Version 1.0.2

Description The AlphaMissense publication 
<https://www.science.org/doi/epdf/10.1126/science.adg7492> outlines how a variant of AlphaFold / DeepMind was used to predict missense variant pathogenicity. Supporting data on Zenodo 
<https://zenodo.org/record/10813168> include, for instance, 71M variants across hg19 and hg38 genome builds. The ‘AlphaMissenseR’ package allows ready access to the data, downloading individual files to DuckDB databases for exploration and integration into *R* and *Bioconductor* workflows.

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URL https://mtmorgan.github.io/AlphaMissenseR/

BugReports https://github.com/mtmorgan/AlphaMissenseR/issues

Depends dplyr

Imports rjsoncons (>= 1.0.1), DBI, duckdb (>= 0.9.1), rlang, curl, 
BiocFileCache, spdl, memoise, BiocBaseUtils, utils, stats, 
methods, whisker

Suggests BiocManager, BiocGenerics, GenomicRanges, GenomeInfoDb, 
AnnotationHub, ensemblpdb, http, tidyr, r3dmol, bio3d, shiny, 
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af_predictions

af_predictions() retrieves information about AlphaFold predictions associated with UniProt accession identifiers.

af_prediction_view() summarizes effects of possible amino acid changes in a single UniProt protein. The changes are displayed on the AlphaFold-predicted structure.

af_colorfunc_by_position() generates a Javascript function to be used in rd3mol::m_set_style() to color residues by position, e.g., when visualizing median predicted pathogenicity.

Usage

af_predictions(uniprot_ids)

af_prediction_view(tbl, bfc = BiocFileCache())

af_colorfunc_by_position(
  tbl,
  pos,
  value,
```r
pos_max = NULL,
palette = colorspace::diverging_hcl(11),
palette_min = NULL,
palette_max = NULL
)
```

**Arguments**

- `uniprot_ids` character() UniProt accession identifiers (uniprot_id in AlphaMissense tables).
- `tbl` A tibble containing information on the UniProt protein and AlphaMissense predicted amino acid effects.
  
  For `av_prediction_view()` the tibble must have columns `uniprot_id`, `protein_variant`, `am_pathogenicity`, and `am_class`, as in tibbles returned by `am_data("hg38")` or `am_data("aa_substitutions")`, for instance. The `uniprot_id` must contain a single unique value.
  
  For `af_colorfunc_by_position()` the tibble must have columns `pos` and `value`, as described below.
- `bfc` An object created with `BiocFileCache::BiocFileCache()`, representing the location used to cache PDB files retrieved by `av_prediction_view()`. The default is the BiocFileCache installation-wide location.
- `pos` the symbol or name of the column in `tbl` containing amino acid residue positions in the protein.
- `value` the symbol or name of the column in `tbl` containing values to be used for coloring amino acid residues in the protein.
- `pos_max` integer(1) the maximum residue position in the protein to be visualized. Default: the maximum value in `pos`.
- `palette` character() vector of colors to be used in visualization. The default (`colorspace::diverging_hcl(11)`) produces colors ranging from blue (low) to red (high).
- `palette_min` numeric(1) the value bounding the minimum palette color. The default is the minimum of `value`; a common value when plotting pathogenicity might be 0.
- `palette_max` numeric(1) the value bounding the maximum palette color. The default is the maximum of `value`; a common value when plotting pathogenicity might be 1.

**Details**

`af_predictions()` queries the prediction endpoint of the AlphaFold API described at [https://alphafold.ebi.ac.uk/api-docs](https://alphafold.ebi.ac.uk/api-docs).

`af_prediction_view()` uses `tbl` to calculate median pathogenicity at each amino acid position, using `am_aa_pathogenicity()`. Predicted protein structure is retrieved from the unique `uniprot_id` using `af_predictions()` and the `pdbUrl` returned by that function. Protein structure is visualized using the `r3dmol https://cran.R-project.org/package=r3dmol` package. Amino acids are colored using `aa_pathogenicity_median` and `af_colorfunc_by_position()` with default palette defined on the interval 0, 1.

`af_colorfunc_by_position()` uses a template mechanism to inject a vector of position-specific colors into a Javascript function used by `r3dmol::m_set_style()`/`r3dmol::m_style_cartoon()`
to color residues by position. Positions for which no color is specified are colored 'gray'. The template can be seen with `AlphaMissenseR:::js_template("colorfunc")`.

Value

`af_predictions()` returns a tibble. Each row represents the AlphaFold prediction associated with the corresponding uniprot accession. Columns include:

- `entryId`: AlphaFold identifier.
- `gene`: gene symbol corresponding to UniProt protein.
- `uniprotAccession`, `uniprotId`, `uniprotDescription`: UniProt characterization. AlphaMissense's `uniprot_id` is AlphaFold's `uniprotAccession`.
- `taxId`, `organismScientificName`: Organism information.
- `uniprotStart`, `uniprotEnd`, `uniprotSequence`: protein sequence information.
- `modelCreatedDate`, `latestVersion`, `allVersions`, `isReviewed`, `isReferenceProteome`: AlphaFold provenance information.
- `cifUrl`, `bcifUrl`, `pdbUrl`: URLs to AlphaFold 3-dimensional molecular representations.
- `paeImageUrl`, `paeDocUrl`: 'Predicted Aligned Error' heat map and underlying data. These can be used to assess the confidence in relative orientation of residues in different domains, as described in part in the AlphaFold FAQ [https://alphafold.ebi.ac.uk/faq](https://alphafold.ebi.ac.uk/faq)

`af_prediction_view()` displays an interactive view of the protein in an RStudio panel or browser tab.

`af_colorfunc_by_position()` returns a character(1) vector representation of the Javascript function, with color vector injected.

Examples

```r
## af_predictions
uniprot_ids <-
  am_data("aa_substitutions") |> 
  dplyr::filter(uniprot_id %like% "P3555%") |> 
  dplyr::distinct(uniprot_id) |> 
  pull(uniprot_id)
af_predictions(uniprot_ids)

## af_prediction_view()
P35557 <-
  am_data("hg38") |> 
  dplyr::filter(uniprot_id == "P35557")
af_prediction_view(P35557)

## no AlphaFold prediction for this protein
P35555 <-
  am_data("aa_substitutions") |> 
  dplyr::filter(uniprot_id == "P35555")
```
tryCatch({
  af_prediction_view(P35555)
}, error = identity)

## af_colorfunc_by_position()

df <- tibble(
  pos = 1 + 1:10, # no color information for position 1
  value = 10:1 / 10
)
colorfunc <- af_colorfunc_by_position(
  df,
  "pos", "value",
  pos_max = 12    # no color information for position 12
)
cat(colorfunc)

## template used for Javascript function

cat(
  AlphaMissenseR:::js_template("colorfunc", colors = "..."),
  "\n"
)

---

**ALPHAMISSENSE_RECORD Retrieve AlphaMissense Resources as DuckDB Databases**

**Description**

ALPHAMISSENSE_RECORD is a constant identifier corresponding to the default version of the AlphaMissense resource to use.

am_browse() opens a web browser at the Zenodo record for the AlphaMissense data.

am_available() reports available datasets in the record.

am_data() retrieves a single key from the AlphahMissense Zenodo site and parses the file into a DuckDB database.

**Usage**

ALPHAMISSENSE_RECORD

am_browse(record = ALPHAMISSENSE_RECORD)

am_available(record = ALPHAMISSENSE_RECORD, bfc = BiocFileCache())

am_data(
  key,
  record = ALPHAMISSENSE_RECORD,
bfc = BiocFileCache(),
as = c("tbl", "tsv")
}

Arguments

record character(1) Zenodo record for the AlphaMissense data resources.
bfc an object returned by BiocFileCache() representing the location where downloaded files and the parsed database will be stored. The default is the 'global' BiocFileCache.
key a character(1) 'key' from the result of am_available(), or a single row of the tibble returned by am_available().
as character(1) type of return value.
  • "tbl": a dbplyr tbl representation of the database resource.
  • "tsv": path to the tsv.gz file representing the resource and downloaded from Zenodo

Format

An object of class character of length 1.

Details

ALPHAMISSENSE_RECORD can be set before the package is loaded with the environment variable of the same name, e.g., Sys.setenv(ALPHAMISSENSE_RECORD = "8208688"). The default is the most recent version (version 2) on 25 September, 2023.

am_data() uses BiocFileCache to download and store the file and the corresponding DuckDB database.

Value

am_available() returns a tibble with columns key, size, and link. The meaning of key must be determined with reference to the information at am_browse().

am_data() returns a dbplyr (database) tibble represented the downloaded and parsed file. Fields in the database are as described on the Zenodo resource page.

Examples

if (interactive())
  am_browse()
  am_available()
  am_data("hg38")

  # close the connection opened when adding the data
Description

`am_aa_pos()` separates protein_variant columns into amino acid 'pos', 'ref', and 'alt' columns.
`am_aa_pathogenicity()` summarizes pathogenicity scores at each protein amino acid position.

Usage

```r
am_aa_pos(tbl)
```

```r
am_aa_pathogenicity(tbl)
```

Arguments

- `tbl` a tibble, usually derived from `am_data("aa_substitutions")`, `am_data("hg38")`, etc. See details.

Details

`tbl` is `collect()`ed before computation, so all rows must fit into memory.

For `am_aa_pos()`, `tbl` must contain a column `protein_variant` with entries in the form "Q465H", as in the AlphaMissense data.

For `am_aa_pathogenicity()`, `tbl` must contain columns `uniprot_id`, `protein_variant`, `am_pathogenicity` and `am_class`. If `am_pos` and friends are not already calculated, then `am_aa_pos()` is called.

Value

`am_aa_pos()` returns the original table with additional columns

- `aa_pos`: the position of the protein variant, as an integer().
- `aa_ref`: the single-character reference amino acid in the protein variant.
- `aa_alt`: the single-character alternate amino acid in the protein variant.

`am_aa_pathogenicity()` returns a tibble with columns

- `uniprot_id`, `aa_pos`, `aa_ref`: the UniProt id, and the position and reference amino acid being summarized
- `aa_pathogenicity_n`, `aa_pathogenicity_mean`, `aa_pathogenicity_median`, `aa_pathogenicity_min`, `aa_pathogenicity_max`: the number, average, median, minimum, and maximum of the pathogenicity scores at each amino acid position.
- `aa_pathogenicity_mode`: the modal `am_class` at the amino acid position, as a factor. Tied mode is assigned to lower pathogenicity.
Examples

\[
P35557 \leftarrow \text{am_data("hg38") |> filter(uniprot_id %in% "P35557")}
\]

am_aa_pos(P35557)

am_aa_pos(P35557) |> select(
    uniprot_id, POS, REF, ALT, protein_variant, 
    starts_with("aa_"), am_pathogenicity, am_class 
) |> arrange(aa_pos)

am_aa_pathogenicity(P35557)

---

db_connect | Manipulate the Database of Missense Mutations

Description

db_connect() manages connections to AlphaMissense record-specific databases. By default, connections are created once and reused.
db_tables() queries for the names of temporary and regular tables defined in the database.
db_temporary_table() creates a temporary (for the duration of the duckdb connection) table from a tibble.
db_range_join() performs a range join, finding all positions in key within ranges defined by join. The result is stored in table to.
db_disconnect() disconnects the duckdb database and shuts down the DuckDB server associated with the connection. Temporary tables are lost.
db_disconnect_all() disconnects all managed duckdb database connection.

Usage

db_connect(
    record = ALPHAMISSENSE_RECORD, 
    bfc = BiocFileCache(), 
    read_only = TRUE, 
    managed = read_only 
)

db_tables(db = db_connect())

db_temporary_table(db, value, to)
\begin{verbatim}

db_range_join(db, key, join, to)

db_disconnect(db = db_connect())

db_disconnect_all()

Arguments

record character(1) Zenodo record for the AlphaMissense data resources.
bfc an object returned by BiocFileCache() representing the location where downloaded files and the parsed database will be stored. The default is the ‘global’ BiocFileCache.
read_only logical(1) open the connection 'read only'. TRUE protects against overwriting existing data and is the default.
managed logical(1) when TRUE, re-use an existing managed connection to the same database.
db duckdb_connection object, returned by db_connect().
value a data.frame / tibble containing data to be placed in a temporary table, e.g., from a GenomicRanges object to be used in a range join.
to the character(1) name of the table to be created
key a character(1) table name in db containing missense mutation coordinates.
join a character(1) table name in db containing ranges to be used for joining with (filtering) key.

Details

For db_connect(), set managed = FALSE when, for instance, accessing a database in a separate process. Remember to capture the database connection db_unmanaged <- db_connect(managed = FALSE) and disconnect when done ‘db_disconnect(db_unmanaged). Connections are managed by default.

db_temporary_table() overwrites an existing table with name to.
db_range_join() overwrites an existing table to. The table key is usually "hg19" or "hg38" and must have CHROM and POS columns. The table join must have columns CHROM, start and end. Following Bioconductor convention and as reported in am_browse(), coordinates are 1-based and ranges defined by start and end are closed. All columns from both key and join are included, so column names (other than CHROM) cannot be duplicated.
db_disconnect() should be called on each unmanaged connection, and once (to free the default managed connection) at the end of a session.

Value

db_connect() returns an open duckdb_connection to the AlphaMissense record-specific database.
db_tables() returns a character vector of database table names.
db_temporary_table() returns the temporary table as a dbplyr tibble.
db_range_join() returns to (the temporary table created from the join) as a dbplyr tibble.
\end{verbatim}
db_disconnect() returns FALSE if the connection has already been closed or is not valid (via dbIsValid()) or TRUE if disconnection is successful. Values are returned invisibly.

db_disconnect_all() returns the db_disconnect() value for each connection, invisibly.

Examples

db_connect() # default 'read-only' connection
db_rw <- db_connect(read_only = FALSE)

am_data("hg38") # uses the default, 'read-only' connection
db_tables() # connections initially share the same tables
db_tables(db_rw)

## ranges of interest -- the first 200000 bases on chromosomes 1-4.
ranges <- tibble(
  CHROM = paste0("chr", 1:4),
  start = rep(1, 4),
  end = rep(200000, 4)
)
db_temporary_table(db_rw, ranges, "ranges")

db_tables(db_rw) # temporary table available to the db_rw connection...
db_tables() # ...but not to the read-only connection

rng <- db_range_join(db_rw, "hg38", "ranges", "ranges_overlaps")
rng
rng |> count(CHROM) |> arrange(CHROM)

db_disconnect(db_rw) # explicit read-write connection
db_disconnect() # implicit read-only connection

db_disconnect_all()

---

to_GPos

Create GenomicRanges Objects from AlphaMissense Annotations

Description
to_GPos() coerces a tibble derived from am_data("hg19") or am_data("hg38") resources to GenomicRanges GPos objects.

Usage
to_GPos(tbl)
Arguments

tbl  a tibble derived from `am_data("hg19")` or `am_data("hg38")`. The tibble must have columns `CHROM`, `POS`, and `genome`.

Value

to_GPos() returns a GPos object, which can be used in the same way as a GRanges object for range-based filtering and annotation.

Examples

```r
am_data("hg38") |> filter(CHROM == "chr2", POS < 10000000, REF == "G") |> select(-REF) |> to_GPos()
```
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