

# Package ‘RxnSim’

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**Type** Package

**Title** Functions to Compute Chemical and Chemical Reaction Similarity

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**Description** Methods to compute chemical similarity between two or more reactions and molecules. Allows masking of chemical substructures for weighted similarity computations. Uses packages 'rCDK' and 'fingerprint' for cheminformatics functionality. Methods for reaction similarity and sub-structure masking are as described in: Giri et al. (2015) <[doi:10.1093/bioinformatics/btv416](https://doi.org/10.1093/bioinformatics/btv416)>.

**License** GPL-3

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## Description

RxnSim provides methods to compute molecular and reaction similarity. It uses rCDK package (R Interface to the CDK Libraries) and fingerprints package for chemoinformatic routines.

## Details

RxnSim provides methods to compute chemical similarity between two or more reactions and molecules. Molecular similarity is computed based on structural features. Reaction similarity is a function of similarities of participating molecules. The package provides multiple methods to extract structural features as fingerprints (or feature vectors) and similarity metrics. It additionally provides functionality to mask chemical substructures for weighted similarity computations. It uses rCDK and fingerprint packages for cheminformatics functionality.

### User functions:

`rs.compute` computes similarity between two reactions.

`rs.compute.list` computes similarity between all pairs of reactions from two lists.

`rs.compute.sim.matrix` computes pairwise similarity between all reactions in a list.

`rs.compute.DB` computes similarity of a reaction to those in a reaction database (DB) object read from a text file.

`rs.makeDB` reads a text file containing EC Numbers, Reaction Names and Reaction SMILES and converts it into a reaction DB object.

`ms.compute` computes similarity between two molecules.

`ms.compute.sim.matrix` computes pairwise similarity between all molecules in a list.

`rs.clearCache` clears fingerprint cache.

`rs.mask` substitutes given sub-structure in the molecules of a reaction by a user defined mask.

`ms.mask` substitutes given sub-structure in a molecule by a user defined mask.

## Author(s)

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## See Also

`rs.compute`, `ms.compute`

**Examples**

```
# Reaction similarity
rs.compute('CCC0>>CCC=O', 'CC(O)C>>CC(=O)C')

# Metabolite similarity
ms.compute('CCC=O', 'CC(O)C')
```

ms.compute

*Computes Similarity of Molecules***Description**

Computes chemical similarity between two (or more) input molecules.

**Usage**

```
ms.compute (molA, molB, format = 'smiles', standardize = TRUE, explicitH = FALSE,
            sim.method = 'tanimoto', fp.type = 'extended', fp.mode = 'bit', fp.depth = 6,
            fp.size = 1024, fpCached = FALSE)
ms.compute.sim.matrix (molA, format = 'smiles', standardize = TRUE, explicitH = FALSE,
                       sim.method = 'tanimoto', fp.type = 'extended', fp.mode = 'bit', fp.depth = 6,
                       fp.size = 1024, clearCache = TRUE)
ms.compute.PCA(molA, format = 'smiles', standardize = TRUE, explicitH = FALSE,
               fp.type = 'extended', fp.mode = 'bit', fp.depth = 6, fp.size = 1024,
               clearCache = TRUE)
```

**Arguments**

|             |   |
|-------------|---|
| molA        | input molecule in SMILES format or name (with path) of MDL MOL file.<br>ms.compute.sim.matrix accepts list of molecules as input.   |
| molB        | input molecule in SMILES format or name (with path) of MDL MOL file.  |
| format      | specifies format of input molecule(s). Molecule(s) can be provided in one of following formats: 'SMILES' (default) or 'MOL'.  |
| standardize | suppresses all explicit hydrogen if set as TRUE (default).  |
| explicitH   | converts all implicit hydrogen to explicit if set as TRUE. It is set as FALSE by default.   |
| sim.method  | similarity metric to be used to evaluate molecule similarity. Allowed types include:<br>'simple', 'jaccard', 'tanimoto' (default), 'russelrao', 'dice', 'rodgerstanimoto', 'achiai', 'cosine', 'kulczynski2', 'mt', 'baroniurbanibuser', 'tversky', 'robust', 'hamann', 'pearson', 'yule', 'mcconnaughey', 'simpson', 'jaccard-count' and 'tanimoto-count'. |
| fp.type     | fingerprint type to use. Allowed types include:<br>'standard', 'extended' (default), 'graph', 'estate', 'hybridization', 'maccs', 'pubchem', 'kr', 'shortestpath', 'signature' and 'circular'.  |

|            |   |
|------------|---|
| fp.mode    | fingerprint mode to be used. It can either be set to 'bit' (default) or 'count'.  |
| fp.depth   | search depth for fingerprint construction. This argument is ignored for 'pubchem', 'maccs', 'kr' and 'estate' fingerprints.   |
| fp.size    | length of the fingerprint bit string. This argument is ignored for 'pubchem', 'maccs', 'kr', 'estate', 'circular' (count mode) and 'signature' fingerprints.                            |
| fpCached   | boolean that enables fingerprint caching. It is set to FALSE by default.  |
| clearCache | boolean that resets the cache before (and after) processing molecule lists. It is set to TRUE by default. Cache can also be explicitly cleared by using <a href="#">rs.clearCache</a> . |

### Details

See [rs.compute](#) functions, for details for fingerprints and similarity matrices. `ms.compute` can use fingerprint caching by enabling `fpCached` option. `ms.compute` and `ms.compute.sim.matrix` use same cache as `rs.compute` and other functions in the package. `ms.compute.PCA` computes PCA based on the fingerprints using `prcomp` function.

### Value

Returns similarity value(s).

`ms.compute` returns a similarity value.

`ms.compute.sim.matrix` returns a  $m \times m$  symmetric matrix of similarity values.  $m$  is the length of the input list.

`ms.compute.PCA` returns `prcomp` object.

### Note

Fingerprint cache stores fingerprints generated for a molecule index based on its SMILES. When caching is enabled, the fingerprint for a molecule, if present, is retrieved from the cache. The parameters pertaining to fingerprint generation are thus ignored. If the fingerprint for the molecule is not already cached, fingerprint based on the input parameters is generated and stored in the cache.

### Author(s)

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### See Also

[rs.compute](#), [rs.clearCache](#)

### Examples

```
ms.compute('N', '[H]N([H])[H]', standardize = FALSE)
```

---

|               |                                 |
|---------------|---------------------------------|
| rs.clearCache | <i>Clears Fingerprint Cache</i> |
|---------------|---------------------------------|

---

**Description**

Clears fingerprint cache. rs.clearCache should be called before fingerprint method (or related properties) are modified.

**Usage**

```
rs.clearCache()
```

**Value**

No return value

**Author(s)**

Varun Giri <varungiri@gmail.com>

**See Also**

[rs.compute](#), [ms.compute](#)

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|            |   |
|------------|---|
| rs.compute | <i>Computes Similarity of Reactions</i> |
|------------|---|

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**Description**

Computes similarity between two (or more) input reactions.

rs.compute computes similarity of two reactions.

rs.compute.list computes similarity of two lists of reactions.

rs.compute.sim.matrix computes similarity of reactions in a list.

rs.compute.DB computes similarity of a reaction against a database (parsed from text file).

**Usage**

```
rs.compute (rxnA, rxnB, format = 'rsmi', standardize = TRUE, explicitH = FALSE,
            reversible = TRUE, algo = 'msim', sim.method = 'tanimoto',
            fp.type = 'extended', fp.mode = 'bit', fp.depth = 6, fp.size = 1024,
            verbose = FALSE, fpCached = FALSE)
rs.compute.list (rxnA, rxnB, format = 'rsmi', standardize = TRUE, explicitH = FALSE,
                reversible = TRUE, algo = 'msim', sim.method = 'tanimoto',
                fp.type = 'extended', fp.mode = 'bit', fp.depth = 6, fp.size = 1024,
                clearCache = TRUE)
```

```
rs.compute.sim.matrix(rxnA, format = 'rsmi', standardize = TRUE, explicitH = FALSE,
                      reversible = TRUE, algo = 'msim', sim.method = 'tanimoto',
                      fp.type = 'extended', fp.mode = 'bit', fp.depth = 6, fp.size = 1024,
                      clearCache = TRUE)
rs.compute.DB(rxnA, DB, format = 'rsmi', ecrange = '*', reversible = TRUE,
              algo = 'msim', sim.method = 'tanimoto', sort = TRUE, fpCached = FALSE)
```

## Arguments

|             |  |
|-------------|--|
| rxnA        | input reaction in RSMI format or name (with path) of MDL RXN file. <code>rs.compute.list</code> and <code>rs.compute.sim.matrix</code> accept list of reactions as input.  |
| rxnB        | input reaction in RSMI format or name (with path) of MDL RXN file. <code>rs.compute.list</code> accepts list of reactions as input.  |
| DB          | parsed database object as returned by <code>rs.makeDB</code> .   |
| format      | specifies format of input reaction(s). Reaction(s) can be provided in one of following formats: 'RSMI' (default) or 'RXN'.   |
| ecrange     | EC number(s) search pattern while comparing against reaction DB. * is used as wildcard. E.g., 1.2.1.* will restricted search to all reactions with EC numbers starting with 1.2.1.-.   |
| standardize | suppresses all explicit hydrogen if set as TRUE (default).   |
| explicitH   | converts all implicit hydrogen to explicit if set as TRUE. It is set as FALSE by default.  |
| reversible  | boolean that indicates reversibility of input reaction(s). If set as TRUE (default), reaction(s) are aligned by comparing them in forward direction and by reversing one of them to compute maximum similarity value.  |
| algo        | reaction similarity algorithm to be used. One of following algorithms can be used: 'msim' (default), 'msim_max', 'rsim' and 'rsim2'. See description for the details of the algorithms.  |
| sim.method  | similarity metric to be used to evaluate reaction similarity. Allowed types include: 'simple', 'jaccard', 'tanimoto' (default), 'russelrao', 'dice', 'rodgerstanimoto', 'achiai', 'cosine', 'kulczynski2', 'mt', 'baroniurbanibuser', 'tversky', 'robust', 'hamann', 'pearson', 'yule', 'mcconnaughey', 'simpson', 'jaccard-count' and 'tanimoto-count'. |
| fp.type     | fingerprint type to use. Allowed types include: 'standard', 'extended' (default), 'graph', 'estate', 'hybridization', 'maccs', 'pubchem', 'kr', 'shortestpath', 'signature' and 'circular'.  |
| fp.mode     | fingerprint mode to be used. It can either be set to 'bit' (default) or 'count'.   |
| fp.depth    | search depth for fingerprint construction. This argument is ignored for 'pubchem', 'maccs', 'kr' and 'estate' fingerprints.  |
| fp.size     | length of the fingerprint bit string. This argument is ignored for the 'pubchem', 'maccs', 'kr', 'estate', 'circular' (count mode) and 'signature' fingerprints.   |

|            |   |
|------------|---|
| verbose    | boolean that enables display of detailed molecule pairing and reaction alignment (and respective similarity values). The argument is ignored for 'rsim2' algorithm. |
| sort       | boolean that enables rs.compute.DB to return data frame sorted based upon decreasing value of similarities.   |
| fpCached   | boolean that enables fingerprint caching. It is set to FALSE by default.  |
| clearCache | boolean that resets the cache before (and after) processing reaction lists. It is set to TRUE by default. Cache can also be explicitly cleared using rs.clearCache. |

## Details

**RxnSim** implements four algorithms to compute reaction similarity, namely msim, msim\_max, rsim and rsim2.

msim is based on individual similarities of molecules in two reactions. First, each reactant (product) of a reaction is paired with an equivalent (similar) reactant (product) of the other reaction based on pairwise similarity values using hierarchical grouping. A 0 similarity value is assigned to each unpaired molecule. Reaction similarity is then computed by averaging the similarity values for each pair of equivalent molecule(s) and unpaired molecule(s). Molecule equivalences computed can be reviewed using verbose mode in rs.compute.

msim\_max reaction similarity is computed in the same way as described for msim except that the unpaired molecules are not used for computing average.

rsim is based on cumulative features of reactant(s) and product(s) of two reactions. Each reaction is represented by two fingerprints, one each for the reactants and another for products. Reaction similarity is computed by averaging similarity values obtained by comparing reactants fingerprint and products fingerprints.

rsim2 is based on cumulative features of all molecules in a reaction forming a reaction fingerprint. Reaction similarity is computed based on the reaction fingerprints of two reactions.

For reversible reactions (reversible = TRUE), apart from comparing reactions in the forward direction they are also compared by reversing one of the reactions. The greater of the two similarity values is reported.

### Fingerprint Caching

rs.compute and rs.compute.DB functions can use fingerprint caching. If fpCached is set as TRUE, cache is queried first before generating fingerprints. Any new fingerprint generated is stored in the cache. Setting fpCached = FALSE makes no change to cache. Cache can be cleared by calling [rs.clearCache](#).

rs.compute.list and rs.compute.sim.matrix functions internally use caching. To ensure consistency of fingerprints, [rs.clearCache](#) is called internally. Use clearCache = FALSE to override this behaviour; it will use current state of cache and add new fingerprints to it.

Same cache is used for all functions.

**Similarity metric included in RxnSim.** These metric (except jaccard-count and tanimoto-count) are derived from [fingerprint package](#).

| ID     | Name             | Remarks |
|--------|------------------|---------|
| simple | Sokal & Michener | bit     |

|                   |                     |               |
|-------------------|---------------------|---------------|
| jaccard           | Jaccard             | bit           |
| tanimoto          | Tanimoto (bit)      | bit and count |
| jaccard-count     | Jaccard (count)     | count         |
| tanimoto-count    | Tanimoto (count)    | count ^       |
| dice              | Dice (bit)          | bit and count |
| russelrao         | Russel And Rao      | bit           |
| rodgerstanimoto   | Roger And Tanimoto  | bit           |
| achiai            | Ochiai              | bit           |
| cosine            | Cosine              | bit           |
| kulczynski2       | Kulczynski 2        | bit           |
| mt                | Modified Tanimoto   | bit           |
| baroniurbanibuser | Baroni-Urbani/Buser | bit           |
| robust            | Robust (bit)        | bit and count |
| tversky           | Tversky*            | bit           |
| hamann            | Hamann              | bit           |
| pearson           | Pearson             | bit           |
| yule              | Yule                | bit           |
| mcconnaughey      | McConnaughey        | bit           |
| simpson           | Simpson             | bit           |

\*Tversky coefficients can be specified by combining them into a vector, e.g., `c('tversky', a, b)`.

tanimoto (bit), dice (bit) and robust (bit) compute similarity of feature vectors (count mode) by translating them to equivalent fingerprint vectors. Default similarity metric used is tanimoto.

**List of fingerprints included in RxnSim.** These are derived from [rCDK package](#).

| ID            | Name of the Fingerprint | Mode          |
|---------------|-------------------------|---------------|
| standard      | Standard                | bit           |
| extended      | Extended                | bit           |
| estate        | EState                  | bit           |
| graph         | Graphonly               | bit           |
| hybridization | Hybridization           | bit           |
| maccs         | MACCS                   | bit           |
| pubchem       | Pubchem                 | bit           |
| kr            | Klekota-Roth            | bit           |
| shortestpath  | Shortestpath            | bit           |
| signature     | Signature               | count         |
| circular      | Circular                | bit and count |

## Value

`rs.compute` returns a similarity value.

`rs.compute.list`

returns a  $m \times n$  matrix of similarity values.  $m$  and  $n$  are the length of two input lists respectively.



`rs.compute.sim.matrix`  
returns a  $m \times m$  symmetric matrix of similarity values.  $m$  is the length of the input list.

`rs.compute.DB` returns a data frame.

### Note

While using fingerprint caching (by setting `fpCached = TRUE` in `rs.compute` and `rs.compute.DB` or `clearCache = FALSE` in `rs.compute.list` and `rs.compute.sim.matrix`), ensure that the fingerprints are generated using same parameters values (`fp.type`, `fp.mode`, `fp.depth` and `fp.size`). To reset cache, call [rs.clearCache](#).

`rs.compute.DB` uses same parameter values for creating fingerprint as used for (and stored with) DB object (created using [rs.makeDB](#)) passed as argument.

### Author(s)

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### References

<sup>^</sup> Carbonell, P., Planson, A-G., Fichera, D., & Faulon J-L. (2011) A retrosynthetic biology approach to metabolic pathway design for therapeutic production. *BMC Systems Biology*, **5**:122.

### See Also

[rs.makeDB](#), [rs.clearCache](#), [ms.compute](#)

### Examples

```
# Reaction similarity using msim algorithm
rs.compute(rct1, rct2, verbose = TRUE)
```

---

`rs.makeDB`*Converts Text File to Reaction Database*

---

### Description

Reads and parses input text file containing reaction smiles into reaction database object. The reaction database is used for querying reaction similarity of candidate reactions.

### Usage

```
rs.makeDB (txtFile, header = FALSE, sep = '\t', standardize = TRUE, explicitH = FALSE,
           fp.type = 'extended', fp.mode = 'bit', fp.depth = 6, fp.size = 1024,
           useMask = FALSE, maskStructure, mask, recursive = FALSE)
```

## Arguments

|               |   |
|---------------|---|
| txtFile       | input file containing EC numbers, reaction name and RSMI. See description for format of input file.   |
| header        | boolean to indicate if the input file contains a header. It is set to FALSE by default.   |
| sep           | the field separator character to be used while reading the input file.  |
| standardize   | suppresses all explicit hydrogen if set as TRUE (default).  |
| explicitH     | converts all implicit hydrogen to explicit if set as TRUE. It is set as FALSE by default.   |
| fp.type       | Fingerprint type to use. Allowed types include: 'standard', 'extended' (default), 'graph', 'estate', 'hybridization', 'maccs', 'pubchem', 'kr', 'shortestpath', 'signature' and 'circular'. |
| fp.mode       | fingerprint mode to be used. It can either be set to 'bit' (default) or 'count'.  |
| fp.depth      | search depth for fingerprint construction. This argument is ignored for 'pubchem', 'maccs', 'kr' and 'estate' fingerprints.   |
| fp.size       | length of the fingerprint bit string. This argument is ignored for 'pubchem', 'maccs', 'kr', 'estate', 'circular' (count mode) and 'signature' fingerprints.                                |
| useMask       | boolean to indicate use of masking. If TRUE, each reaction is processed to mask given substructure. See <a href="#">rs.mask</a> for details.  |
| maskStructure | SMILES or SMARTS of the structure to be searched and masked.  |
| mask          | SMILES of structure to be used as mask.   |
| recursive     | if TRUE, all the occurrences of input substructure are replaced recursively.  |

## Details

The parameters used to generate fingerprints are stored in the database object and returned with the parsed data. Same parameter values are used while parsing input reaction in [rs.compute.DB](#).

The input text file should contain following three fields, separated with TAB (or any appropriate field separator). A field can be left blank.

[EC Number]    [Reaction Name]    [Reaction SMILES (RSMI)]

The package comes with a sample reaction database file extracted from Rhea database (Morgat et al., 2015). If no `txtfile` is provided, default sample database file is used:

```
rs.makeDB()
```

A larger dataset containing all reactions from Rhea database (v.83) is also provided with the package.

**Value**

Returns a list, containing parsed input data, reaction fingerprints.

|      |  |
|------|--|
| Data | data frame containing EC Numbers, Reaction Names and RSMI as read from the input file. MaskedRSMI are also included if masking is used.                  |
| FP   | list of molecular fingerprints for each reaction in the input file. These fingerprints are further processed based on the reaction similarity algorithm. |

It also contains the parameter values used for generating fingerprints, viz., `standardize`, `explicitH`, `fp.type`, `fp.mode`, `fp.depth` and `fp.size`.

**Author(s)**

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**References**

Morgat, A., Lombardot, T., Axelsen, K., Aimo, L., Niknejad, A., Hyka-Nouspikel, N., Coudert, E., Pozzato, M., Pagni, M., Moretti, S., Rosanoff, S., Onwubiko, J., Bougueleret, L., Xenarios, I., Redaschi, N., Bridge, A. (2017) Updates in Rhea - an expert curated resource of biochemical reactions. *Nucleic Acids Research*, **45**:D415-D418; doi: 10.1093/nar/gkw990

**See Also**

[rs.compute.DB](#), [rs.mask](#)

---

rs.mask

*Masks a Sub-structure in Input Molecule or Reaction*

---

**Description**

Replaces a sub-structure, provided as SMILES or SMARTS, with the given mask.

`rs.mask` masks input sub-structure in reaction.

`ms.mask` masks input sub-structure in molecule.

**Usage**

```
rs.mask (substructure, mask, reaction, format = 'rsmi', standardize = TRUE,  
        explicitH = FALSE, recursive = FALSE)  
ms.mask (substructure, mask, molecule, format = 'smiles', standardize = TRUE,  
        explicitH = FALSE, recursive = FALSE)
```

### Arguments

|              |   |
|--------------|---|
| substructure | SMILES or SMARTS of the structure to be searched and masked.  |
| mask         | SMILES of structure to be used as mask.   |
| reaction     | Input reaction to be processed.   |
| molecule     | Input molecule to be processed.   |
| format       | specifies format of input reaction/molecule. It can be one of following for a reaction: 'RSMI' or 'RXN'; for a molecule: 'SMILES' or 'MOL'. |
| standardize  | suppresses all explicit hydrogen if set as TRUE (default).  |
| explicitH    | converts all implicit hydrogen to explicit if set as TRUE. It is set as FALSE by default.   |
| recursive    | if TRUE, all the occurrences of input sub-structure are replaced.   |

### Details

The sub-structure is searched in input reaction/molecule and replaced with the mask. All the bonds between identified sub-structure and the remaining atoms are mapped to the mask. If mask contains more than one atom, all the bonds are connected to the last atom in mask. By default, the first identified sub-structure is replaced. To replace all occurrences, recursive should be set to TRUE. Valence is not checked for the mask atom and the final structure.

### Value

Returns SMILES with mask.

### Note

Aromatic form of SMILES of the query sub-structure should be used for masking aromatic structures. Automatic aromaticity perception is not done on query structures.

### Author(s)

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### See Also

[rs.makeDB](#)

### Examples

```
ms.mask('OP(=O)O', '[Cs]', 'O=P(O)(O)OP(=O)(O)OP(=O)(O)OCC3OC(n2cnc1c(ncnc12)N)C(O)C3O')
```

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