Cheminformatics of Drug-like Small Molecules

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December 16, 2013

Cheminformatics Basics

- Structure Formats
- Similarity Searching
- Physicochemical Properties

Hands-on Section

- Compound Import/Export
- Object Classes
- Compound Structure Depictions
- Compound Properties
- Compound Similarity Searching
- Compound Clustering

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Computations on Small Molecule Structures

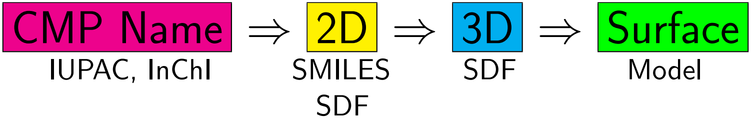
Requirements

- Computer readable representations of chemical structures

Challenges

- Compounds
  - Several connection types, many branch points and/or ring closures
- DNA/protein sequences
  - Linear strings, one connection type, usually no branch points or ring closures

Utility of Structure Formats



CMP Name ⇒ 2D ⇒ 3D ⇒ Surface

IUPAC, InChI

SMILES
SDF

SDF

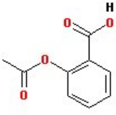
Model

- Nomenclature to uniquely represent chemicals
- Computer representation and manipulation
- Format interconversions
- Representation of stereochemistry and 3D formats

Most Commonly Used Structure Formats

- Chemical nomenclature
  - Trivial names: aspirin, acetylsalicylic acid
  - IUPAC: 2-acetoxybenzoic acid
  - InChI: 1.12Beta/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h1H3,2-5H,(H,11,12)
- Line notations
  - SMILES: CC(=O)Oc1ccccc1C(=O)O
  - Other: WLN, ROSDAL, SLN, etc.
- Connection tables hold 3D & annotation information
  - SDF (structure definition file)
  - MDL Molfile
  - Other: PDB, CML, etc.

Aspirin



Connection Table Formats: SDF and Mol

Molfile: header block and connection table (a, b)

SDfile: extension of Molfile (a, b, c)

- (a) Header block
  - (a1) CMP name or blank line
  - (a2) software, date, 2/3D, ...
  - (a3) blank line
- (b) Connection table (CT)
  - (b1) counts line: n atoms, n bonds, chiral, ...
  - (b2) atom block: x,y,z coordinates, atoms, mass diff., charge, ...
    2D representation when z coordinates all zero
  - (b3) bond block: atom 1, atom 2, bond type, stereo specs, ...
  - (b4) CT delimiter
- (c) Annotation data
  - (c1) <data header>
  - (c2) data
  - (c3) blank line
  - (c4) continues like c1-3
  - (c5) SDF delimiter ($$$$)

Example: SDF Format

```
a1      NSC85228 ethanol 1
a2      APtclserve02230600142D 0 0.00000 0.00000NCI NS
a3
b1      9 8 0 0 0 0 0 0 0 0999 V2000
b2      2.8660 -0.250 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
b2      3.7321 0.2500 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
b2      4.5981 -0.250 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
b2      2.3291 0.0600 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b2      4.1306 0.7249 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b2      3.3335 0.7249 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b2      4.2881 -0.786 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b2      5.1350 -0.560 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b2      4.9081 0.2869 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0
b3      1 2 1 0 0 0 0
b3      2 3 1 0 0 0 0
b3      1 4 1 0 0 0 0
b3      2 5 1 0 0 0 0
b3      2 6 1 0 0 0 0
b3      3 7 1 0 0 0 0
b3      3 8 1 0 0 0 0
b3      3 9 1 0 0 0 0
b4      M END
c1      >< NSC >
c2      85228
c4      >< CAS >
c4      64-17-5
c4      >< SMILES >
c4      CCO
c5      $$$$
```

SMILES

SMILES: Simplified Molecular Input Line Entry System

- Tutorial: http://www.daylight.com/smiles/smiles-intro.html
- Online rendering: http://www.daylight.com/daycgi/depict
- Non-canonical SMILES for manual entry
- Canonical SMILES needs to be computer generated
- Canonicalization: single ('correct') representation of several posibilities
    - OCC - ethanol
    - CCO - ethanol
- Canonical format important for databases

SMILES Rules 1

C

Methane: CH4. Hydrogens are added according to valence rules.

N-C=O

Formamide. Single '-', double '=', triple '#' and aromatic bond ':'.

NC=O

Formamide. Bonds do not need to be specified in unambiguous cases.

NC(CO)=O

2-hydroxyacetamide. Side-chains of branch points in parentheses. The leftmost atom inside parentheses is attached to the atom to the left of the parentheses.

C1CCNCC1

Piperidine. If there is a ring, a matching pair of digits means that the two atoms to the left of the digits are bonded.

SMILES Rules 2

c1ccccc1O

Phenol. Aromatic atoms are represented as lowercase letters. Note also that the bonds default to aromatic and single, as appropriate.

[Pb]

Lead. The typical organic atoms, B, C, N, O, P, S, F, Cl, Br, are drawn without brackets. All other elements must have square brackets, and all their bonds including hydrogens must be specified.

[OH-]

Unusual valence and charge are represented in square brackets '[]'.

c1ccccc1[N+](=O)[O-]

Nitrobenzene. Another example using square brackets to be specific about charge location.

SMILES Rules 3

[Na+].[O-]c1ccccc1

Sodium phenoxide. The '.' (period or "dot") is used to represent disconnections.

[13CH4]

Isotopes are specified in brackets by prefixing the desired integral atomic mass. Connected hydrogens must be specified in brackets.

F/C=C/F

Trans-difluoroethene. Cis/trans configurations around double bonds are specified by slashes: 'C/C=C\C' (cis) and 'C/C=C/C' (trans).

N[C@@H](C)C(=O)O

L-alanine (from N, H-methyl-carboxy appear clockwise). Chirality is specified with '@' and '@@'. @ means anti-clockwise and @@ means clockwise.

N[C@H](C)C(=O)O

D-alanine (from N, H-methyl-carboxy appear anti-clockwise).

SMARTS Is a Query Expression System for SMILES

SMARTS: SMiles ARbitrary Target Specification

- Motivation: superset of SMILES to expresses molecular patterns
- Regular expression system for molecules represented in SMILES format

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Small Molecule Similarity Concepts

How to define similarities between compounds?

- Identical structure search
- Substructure and superstructure searches
- 2D fragment similarity searching
- 3D similarity searches (*e.g.* pharmacophore searching)
- Graph-based approaches (*e.g.* maximum common substructure: MCS)
- Many additional methods

2D Fragment Similarity Search Methods

Involve two major steps

- Encode structural descriptors from compounds
  - *e.g.* structural keys, fingerprints, atom pairs
- Similarity measure for encoded descriptors
  - *e.g.* Tanimoto coefficient, Euclidean

Structural Keys

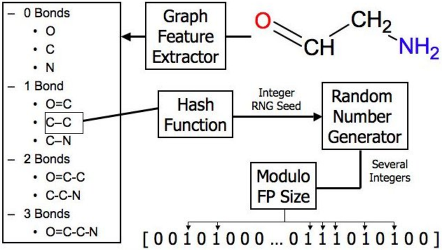
- Structural descriptors are based on lookup library of known ”functional” substructures.
- Pre-compute presence of relevant substructures up front and encode them in bit-vector.
- Example of structural keys:
  - Presence of atoms (C, N, O, S, Cl, Br, etc.)
  - Ring systems
  - Aromatic, Phenol, Alcohol, Amine, Acid, Ester, ...
- Disadvantages:
  - Lookup library tends to be incomplete.
  - Sparsely populated vectors.

Fingerprints

- Fingerprints are generated directly from the molecule itself and not from a reference set of substructures.
- The algorithm examines each molecule and generates the following patterns:
    - One for each atom.
    - One representing each atom and its nearest neighbors (plus the bonds that join them).
    - One representing each group of atoms and bonds connected by paths up to 2, 3, 4, ... bonds long.
    - For example, the molecule OC=CN would generate the following patterns:
        - 0-bond paths: C, O, N
        - 1-bond paths: OC, C=C, CN
        - 2-bond paths: OC=C, C=CN
        - 3-bond paths: OC=CN,

Fingerprints

- No pre-defined patterns.
- Record/counts presence or absence of structural fragments.
- Patterns are often encoded into fixed length (binary) vectors for fast similarity searching.
- Abstract, hard to traceback meaning of individual bits.



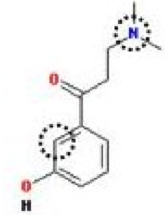
⇓

Database of binary fingerprints

Atom Pair and Atom Sequence Similarity Searching

- Like fingerprints atom pairs are generated directly from the molecule itself and not from a reference set of substructures (Chen and Reynolds, 2002).
- Atom pairs are defined by:
  - the length of the shortest bond path between two atoms,
  - while the terminal atoms in this path are described by:
    - their element type
    - their number of pi electrons
    - their number of non-hydrogen neighbors
  - Example: C12N03_06

Example



- Atom sequences:
  - similar to atom pairs, but all atoms in bond path are described.
  - Example: C12C13C13C02C02N03
- Conversion of atom pairs/sequences to binary vectors of constant length is usually not performed, but would be possible.

Similarity Coefficients

1. Euclidean

$$\sqrt{\frac{c+d}{a+b+c+d}} \tag{1}$$

2. Tanimoto coefficient

$$\frac{c}{a+b+c} \tag{2}$$

3. Simpson coefficient

$$\frac{c}{min((a+c),(b+c))} \tag{3}$$

   NA

4. Many more similarity coefficients (Holliday et al., 2003)

Legend for variables:

a: count of features in CMP A but not in CMP B

b: count of features in CMP B but not in CMP A

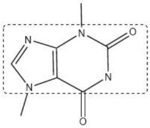
c: count of features in both CMP A and CMP B

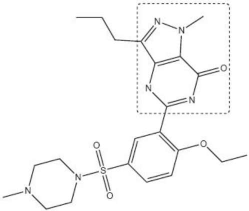
d: count of features absent in CMP A and CMP B

α and β: weighting variables

MCS-based Similarity Concepts

- Graph-based algorithms that find maximum common substructure (MCS) shared among two molecules
- Flexible MCS matching algorithm implemented in *fmcsR* Link allows bond and atom mismatches.
- Major advantage: identification of local similarities





Alternatives: 3D Searches & Docking

Conformer Predictions

Prediction of the most stable conformers in 3D space.

3D Searches

Uses shape and topological indices to query a 3D conformer database.

3D Substructure searches

Related to pharmacophore searches

Docking

Computational modeling of the possible binding modes of a ligand to a target site.

Important Compound Databases

- PubChem
- DrugBank
- ChemBank
- ChEMBL
- Many more

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Compound Descriptors

Structural descriptors

- Atom pairs, fingerprints
- many others

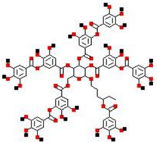
Property descriptors

- Formula
- Molecular weight
- Octanol/Water partition coefficient (logP)
- Hydrogen Bond Acceptors
- Hydrogen Bond Donors
- Acidic groups
- Rotatable bonds
- over 300-3000 additional ones

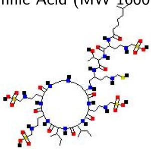
Clustering Methods

- Principal component analysis (PCA)
  - Reduction technique of multivariate data to principal compoments to identify hidden variances
- Multidimensional scaling
  - Displays distance matrix of objects in spacial plot
- Hierarchical Clustering
  - Iterative joining of items by decreasing similarity
- Jarvis-Patrick Clustering
  - Joins items based on intersects among nearest neighbor vectors
- Binning Clustering
  - Uses similarity cutoff for grouping of items
- Many additional clustering algorithms are being used in this field.

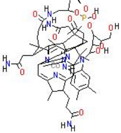
Example: PCA of Small Molecule Properties



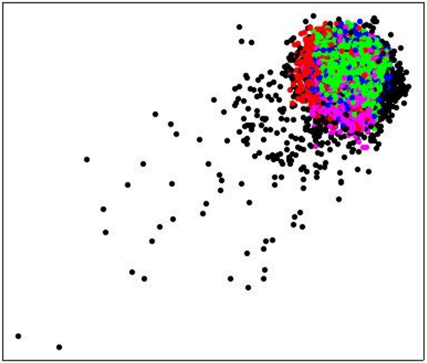
Tannic Acid (MW 1600)



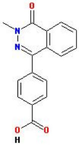
Colistimethate (MW 1400)



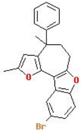
Cobalamine (MW 1100)



Comb1 Comb2 Comb3 Comb4 Bioact



56421 (MW 270)



19737 (MW 390)

Cheminformatics in R

Why cheminformatics in R?

- Open source
- Efficient data structures and graphics utilities
- Access to many clustering and machine learning algorithms
- Integration with bioscience packages

R packages for cheminformatics

- Bioconductor
  - *ChemmineR* Link (Cao et al., 2008)
  - *eiR* Link
  - *fmcsR* Link (Wang et al., 2013)
  - *ChemmineOB* Link: R interface to subcomponents of *OpenBabel*
  - *bioassayR* Link: screening data analysis
  - *ChemMine Tools* Link: web interface to Chemmine utilities (Backman et al., 2011)
- CRAN
  - *rcdk* Link
  - *rpubchem* Link

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Import of SD Files

Download R code Link for exercises and open in RStudio session

```
> download.file(url="http://faculty.ucr.edu/~tgirke/HTML_Presentations/Manuals/Workshop_Dec_12_16_2013/Rcheminf
```

Loading the *ChemmineR* package and its documentation

```
> library("ChemmineR") # Loads the package
```

Accessing *ChemmineR* PDF manual and help documents

```
> library(help="ChemmineR") # Lists all functions and classes
> vignette("ChemmineR") # Opens PDF manual from R
> ?MW # Opens help for MW function
```

Import SD file into *SDFset* object

```
> sdfset <- read.SDFset("http://faculty.ucr.edu/~tgirke/Documents/R_BioCond/Samples/
> sdfset # Returns summary of SDFset
> valid <- validSDF(sdfset) # Identifies invalid SDFs in SDFset objects
> sdfset <- sdfset[valid] # Removes invalid SDFs, if there are any
```

Load sample SD file provided by package

```
> data(sdfsample)
> sdfset <- sdfsample
> sdfset # Returns summary of SDFset

An instance of "SDFset" with 100 molecules
```

Export Molecule Structures to SD Files

Write first 4 molecules to SD file

```
> write.SDF(sdfset[1:4], file="sub.sdf", sig=TRUE)
> list.files(pattern="sub.sdf")
```

```
[1] "sub.sdf"
```

Write all molecules to several files each containing 50 entries

```
> write.SDFsplit(x=sdfset, filetag="myfile", nmol=50)
```

```
  from  to          filename
1    1  50 myfile001_050.sdf
2   51 100 myfile051_100.sdf
```

Reimports newly created SD file

```
> sdfsetsub <- read.SDFset("sub.sdf")
> sdfsetsub
```

```
An instance of "SDFset" with 4 molecules
```

Import/Export of SMILES Strings

Load SMILES set provided by package

```
> data(smisample); smiset <- smisample
> smiset
An instance of "SMIset" with 100 molecules
> smiset[[1]]
An instance of "SMI"
[1] "O=C(NC1CCCC1)CN(c1cc2OCCOc2cc1)C(=O)CCC(=O)Nc1noc(c1)C"
> view(smiset[1:2])
$`650001`
An instance of "SMI"
[1] "O=C(NC1CCCC1)CN(c1cc2OCCOc2cc1)C(=O)CCC(=O)Nc1noc(c1)C"

$`650002`
An instance of "SMI"
[1] "O=c1[nH]c(=O)n(c2nc(n(CCCc3ccccc3)c12)NCCCO)C"
```

Write SMIset to file, with and without compound identifiers

```
> write.SMI(smiset[1:4], file="sub.smi", cid=TRUE)
> write.SMI(smiset[1:4], file="sub.smi", cid=FALSE)
```

Format interconversions

```
> library(ChemmineOB) # Requries OpenBabel
> mysdf <- smiles2sdf(smiset)
> mysmi <- sdf2smiles(mysdf)
```

Exercise I: Import/Export

Task 1 Open the PubChem site Link and search for 'p450 inhibitor'. Download the resulting 15 query hits to an SD file named 'p450.sdf' using the 'Structure Download' option on the right.

Task 2 Import the 'p450.sdf' into your R session. Here is a backup Link of this file in case there are difficulties with the PubChem site.

Task 3 Check in R the number of compounds stored in 'p450.sdf'.

Task 4 Write the structures in inversed order back to an SD file.

Task 5 Write the structures to several SD files each containing 5 molecules.

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Most Important S4 Objects in *ChemmineR*

Molecular structure containers

SDF: container for single molecule imported from an SD file

SDFset: container for many SDF objects; most important container for end user

SMI: container for a single SMILES string

SMIset: container for many SMILES strings

Structure descriptor containers

AP: container for atom pair (AP) descriptors of a single molecule

APset: container for many AP objects

FP: container for fingerprint of a single molecule

FPset: container for fingerprints of many molecules

Important methods operating on *SDFset*-type containers

- Object slots: `cid`, `header`, `atomblock`, `bondblock`, `datablock`
- Structure depiction: `plot`

Coerce one class to another

- Standard syntax `as(..., "...")` works in most cases. For details see R help with *?”SDFset-class”*.

Working with SDF/SDFset Classes

Several methods are available to return the different data components of *SDF/SDFset* containers in batches. The following examples list the most important ones.

```
> view(sdfset[1:4]) # Summary view of several molecules
> length(sdfset) # Returns number of molecules
> sdfset[[1]] # Returns single molecule from SDFset as SDF object
> sdfset[[1]][[2]] # Returns atom block from first compound as matrix
> sdfset[[1]][[2]][1:4,]
> c(sdfset[1:4], sdfset[5:8]) # Concatenation of several SDFsets
```

The grepSDFset function allows string matching/searching on the different data components of an *SDFset*. By default the function returns a SDF summary of the matching entries. Alternatively, an index of the matches can be returned with the setting *mode="index"*.

```
> grepSDFset("650001", sdfset, field="datablock", mode="subset")
>    # To return index, set mode="index")
```

Accessing *SDF/SDFset* Components

Methods for retrieving header, atom, bond and data blocks

```
> atomblock(sdf); sdf[[2]]; sdf[["atomblock"]]
>     # All three methods return the same component
> header(sdfset[1:4])
> atomblock(sdfset[1:4])
> bondblock(sdfset[1:4])
> datablock(sdfset[1:4])
```

Utilities to manage compound IDs and to keep them unique

```
> sdfid(sdfset[1:4])

[1] "650001" "650002" "650003" "650004"

>     # Retrieves CMP IDs from Molecule Name field in header block.
> cid(sdfset[1:4])

[1] "CMP1" "CMP2" "CMP3" "CMP4"

>     # Retrieves CMP IDs from ID slot in SDFset.
> unique_ids <- makeUnique(sdfid(sdfset))

[1] "No duplicates detected!"

>     # Creates unique IDs by appending a counter to duplicates.
> cid(sdfset) <- unique_ids # Assigns uniquified IDs to ID slot
```

Exercise II: `SDFset` Containers

Task 1 Assign custom names to ID slot in `SDFset` and export object to SD file so that the custom IDs are used as IDs in the header block.

Task 2 Extract the `bondblock` of all structures in an *SDFset*, `rbind` them with `do.call` and write the resulting `matrix` to a tabular file.

Task 3 Replace `atomblock` of first molecule in `SDFset` with `atomblock` of second molecule. Check the result with "==".

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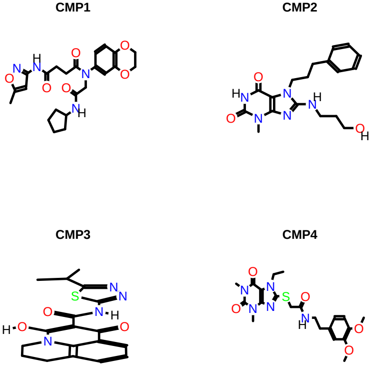
Rendering Chemical Structure Images

Plot compound Structures with R's graphics device

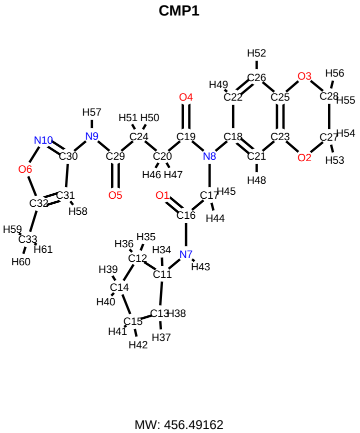
```
> data(sdfsample); sdfset <- sdfsample
> plot(sdfset[1:4], print=FALSE) # print=TRUE returns SDF summaries
```



Customize Structure Rendering

Show atom block position numbers next to the atom symbols. For more details, consult help documentation with `?plotStruc` or `?plot`.

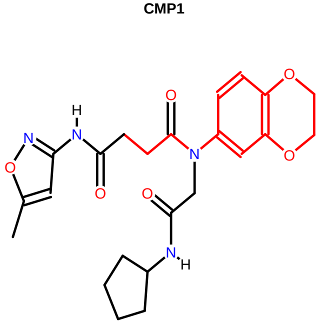
```
> plot(sdfset["CMP1"], atomnum = TRUE,  noHbonds=F , no_print_atoms = "",
+       atomcex=0.8, sub=paste("MW:", MW(sdfsample["CMP1"])), print=FALSE)
```



Substructure Coloring

Substructure highlighting by atom numbers

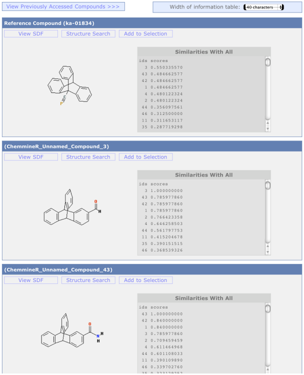
```
> plot(sdfset[1], print=FALSE, colbonds=c(22,26,25,3,28,27,2,23,21,18,8,19,20,24))
```



Online Structure Viewing with ChemMine Tools

Plot structures using web service ChemMine Tools:

> sdf.visualize(sdfset[1:4])



View Previously Accessed Compounds >>>
Width of information table: 40 characters

Reference Compound (ka-01834)

Similarities With All

```
ids scores
  3 0.550335570
 43 0.484662577
 42 0.484662577
  1 0.484662577
  4 0.480122324
  2 0.480122324
 44 0.356097561
 46 0.312500000
 11 0.311653117
 35 0.287719298
```

(ChemmineR_Unnamed_Compound_3)

Similarities With All

```
ids scores
  3 1.000000000
 43 0.785977860
 42 0.785977860
  1 0.785977860
  2 0.766423358
  4 0.646258503
 44 0.561797753
 11 0.415204678
 35 0.390151515
 46 0.368539326
```

(ChemmineR_Unnamed_Compound_43)

Similarities With All

```
ids scores
 43 1.000000000
 42 0.840000000
  1 0.840000000
  3 0.785977860
  2 0.709459459
  4 0.611464968
 44 0.601108033
 11 0.390109890
 46 0.339702760
```

Figure: Visualization page created by calling `sdf.visualize`.

Exercise III: Rendering Compound Structures

Task 1 Plot the structures of compound IDs "42631481", "42631375", "42631371" and "42631260" of the `p450 SDFset` that you created in Exercise I.

Task 2 Render the same structures online with Chemmine Tools.

Outline

Cheminformatics Basics

- Structure Formats
- Similarity Searching
- Physicochemical Properties

Hands-on Section

- Compound Import/Export
- Object Classes
- Compound Structure Depictions
- Compound Properties
- Compound Similarity Searching
- Compound Clustering

Atom Count Table

Several methods and functions are available to compute basic compound descriptors, such as molecular formula (MF), molecular weight (MW), and frequencies of atoms and functional groups. In many of these functions, it is important to set addH=TRUE in order to include/add hydrogens that are often not specified in an SD file.

```
> propma <- atomcountMA(sdfset, addH=FALSE)
> propma[1:4,]
```

```
      C  H N O S F Cl
CMP1 23 28 4 6 0 0  0
CMP2 18 23 5 3 0 0  0
CMP3 18 18 4 3 1 0  0
CMP4 21 27 5 5 1 0  0
```

Data frame provided by library containing atom names, atom symbols, standard atomic weights, group and period numbers.

```
> data(atomprop)
> atomprop[1:4,]
```

```
  Number      Name Symbol Atomic_weight Group Period
1      1  hydrogen      H      1.007940     1      1
2      2    helium     He      4.002602    18      1
3      3   lithium     Li      6.941000     1      2
4      4 beryllium     Be      9.012182     2      2
```

Molecular Weight, Formula and Functional Groups

Compute MW and formula

```
> MW(sdfset[1:4], addH=FALSE)
```

```
    CMP1     CMP2     CMP3     CMP4 
456.4916 357.4069 370.4255 461.5346 
```

```
> MF(sdfset[1:4], addH=FALSE)
```

```
        CMP1          CMP2          CMP3          CMP4 
 "C23H28N4O6"  "C18H23N5O3" "C18H18N4O3S" "C21H27N5O5S" 
```

Enumerate functional groups

```
> groups(sdfset[1:4], groups="fctgroup", type="countMA")
```

```
     RNH2 R2NH R3N ROPO3 ROH RCHO RCOR RCOOH RCOOR ROR RCCH RCN
CMP1    0    2   1     0   0    0    0     0     0   2    0   0
CMP2    0    2   2     0   1    0    0     0     0   0    0   0
CMP3    0    1   1     0   1    0    1     0     0   0    0   0
CMP4    0    1   3     0   0    0    0     0     0   2    0   0
```

Aggregate Many Molecular Properties

Combine MW, MF, charges, atom counts, functional group counts and ring counts in one data frame

```
> propma <- data.frame(MF=MF(sdfset, addH=FALSE), MW=MW(sdfset, addH=FALSE),
+                      Ncharges=sapply(bonds(sdfset, type="charge"), length),
+                      atomcountMA(sdfset, addH=FALSE), groups(sdfset,
+                      type="countMA"), rings(sdfset, upper=6, type="count",
+                      arom=TRUE))
> propma[1:4,]
```

```
              MF       MW Ncharges  C  H N O S F Cl RNH2 R2NH R3N ROPO3 ROH RCHO RC
CMP1  C23H28N4O6 456.4916        0 23 28 4 6 0 0  0    0    2   1     0   0    0
CMP2  C18H23N5O3 357.4069        0 18 23 5 3 0 0  0    0    2   2     0   1    0
CMP3 C18H18N4O3S 370.4255        0 18 18 4 3 1 0  0    0    1   1     0   1    0
CMP4 C21H27N5O5S 461.5346        0 21 27 5 5 1 0  0    0    1   3     0   0    0
```

Properties from OpenBabel with *ChemmineOB*

Computes logP, HBA, HBD and other useful properties

```
> library(ChemmineOB)
> propOB(sdfset)[1:4,]
```

Assign Molecular Properties to SDF Data Block

The following shows an example for assigning the values stored in a matrix (*e.g.* property descriptors) to the data block components in an *SDFset*. Each matrix row will be assigned to the corresponding slot position in the *SDFset*.

```
> datablock(sdfset) <- propma # Works with all SDF components
> datablock(sdfset)[1]
```

```
$CMP1
         MF          MW    Ncharges           C           H           N
"C23H28N4O6"  "456.4916"         "0"        "23"        "28"         "4"
       RCOR       RCOOH       RCOOR         ROR        RCCH         RCN
        "0"         "0"         "0"         "2"         "0"         "0"
```

Convert data block of `SDFset` to matrix.

```
> blockmatrix <- datablock2ma(datablocklist=datablock(sdfset))
> blockmatrix[1:2,1:12]
```

```
     MF           MW         Ncharges C    H    N   O   S   F   Cl  RNH2 R2NH
CMP1 "C23H28N4O6" "456.4916" "0"      "23" "28" "4" "6" "0" "0" "0" "0"  "2"
CMP2 "C18H23N5O3" "357.4069" "0"      "18" "23" "5" "3" "0" "0" "0" "0"  "2"
```

Charges and Missing Hydrogens

The function `bonds` returns information about the number of bonds, charges and missing hydrogens in *SDF* and *SDFset* objects. It is used by many other functions (*e.g.* `MW`, `MF`, `atomcount`, `atomcuntMA` and `plot`) to correct for missing hydrogens that are often not specified in SD files.

```
> bonds(sdfset[[1]], type="bonds")[1:4,]

  atom Nbondcount Nbondrule charge
1    O          2         2      0
2    O          2         2      0
3    O          2         2      0
4    O          2         2      0
```

```
> bonds(sdfset[1:2], type="charge")

$CMP1
NULL

$CMP2
NULL
```

```
> bonds(sdfset[1:2], type="addNH")

CMP1 CMP2
   0    0
```

Ring Perception and Aromaticity Assignment

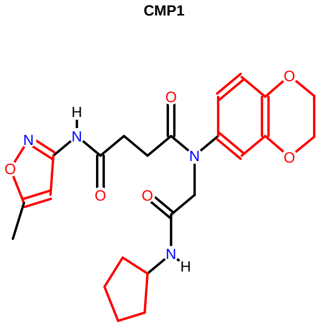
The function `rings` identifies all possible rings in one or many molecules using the exhaustive ring perception algorithm from Hanser et al. (1996). In addition, the function can return all smallest possible rings as well as aromaticity information.

```
> (ringatoms <- rings(sdfset[1], upper=Inf, type="all", arom=TRUE, inner=FALSE))
$RINGS
$RINGS$ring1
[1] "N_10" "O_6"  "C_32" "C_31" "C_30"

$RINGS$ring2
[1] "C_12" "C_14" "C_15" "C_13" "C_11"

$RINGS$ring3
[1] "C_23" "O_2"  "C_27" "C_28" "O_3"  "C_25"

$RINGS$ring4
[1] "C_23" "C_21" "C_18" "C_22" "C_26" "C_25"

$RINGS$ring5
 [1] "O_3"  "C_28" "C_27" "O_2"  "C_23" "C_21" "C_18" "C_22" "C_26" "C_25"


$AROMATIC
ring1 ring2 ring3 ring4 ring5
 TRUE FALSE FALSE  TRUE FALSE
```

Highlight Rings in Structure Image

For visual inspection, the corresponding compound structure can be plotted with the ring bonds highlighted in color.

```
> atomindex <- as.numeric(gsub(".*_", "", unique(unlist(ringatoms))))
> plot(sdfset[1], print=FALSE, colbonds=atomindex)
```



Streaming Through Large SD Files

The sdfStream function allows to stream through SD Files with millions of molecules without consuming much memory. During this process any set of descriptors, supported by *ChemmineR*, can be computed. In addition to descriptor values, the function returns a line index that gives the start and end positions of each molecule in the source SD File. This line index can be used by the downstream read.SDFindex function to retrieve specific molecules of interest from the source SD File without reading the entire file into R.

```
> write.SDF(sdfset, "test.sdf")
> desc <- function(sdfset) {
+         cbind(SDFID=sdfid(sdfset),
+               MW=MW(sdfset),
+               groups(sdfset),
+               rings(sdfset, type="count", upper=6, arom=TRUE)
+         )
+ }
> sdfStream(input="test.sdf", output="matrix.xls", fct=desc, Nlines=1000, silent=TRU
> read.delim("matrix.xls", row.names=1)[1:3,1:10]
```

```
     SDFlineStart SDFlineEnd  SDFID       MW RNH2 R2NH R3N ROPO3 ROH RCHO
CMP1            1        203 650001 456.4916    0    2   1     0   0    0
CMP2          204        381 650002 357.4069    0    2   2     0   1    0
CMP3          382        550 650003 370.4255    0    1   1     0   1    0
```

Exercise IV: Compound Properties

Task 1 Compute for `p450 SDFset` from Exercise I all possible compound properties.

Task 2 Assign the property matrix to the data bock in the corresponding `SDFset`.

Task 3 Export the modified `SDFset` object to an SD file and inspect the result.

Outline

Cheminformatics Basics

- Structure Formats
- Similarity Searching
- Physicochemical Properties

Hands-on Section

- Compound Import/Export
- Object Classes
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- Compound Clustering

Structure Descriptor Containers: `APset/FPset`

The function `sdf2ap` computes atom pair descriptors for one or many compounds (Chen and Reynolds, 2002; Cao et al., 2008). It returns a searchable atom pair database stored in a container of class *APset*, which can be used for structural similarity searching and clustering.

```
> apset <- sdf2ap(sdfset)
> apset
```

```
An instance of "APset" with 100 molecules
```

Most methods working on `SDFset` objects work the same way on descriptor objects.

```
> showClass("APset")
> cid(apset)
> view(apset)
> as(apset, "list")
```

The *FPset* class stores fingerprints of small molecules in a matrix-like representation where every molecule is encoded as a fingerprint of the same type and length.

```
> (fpset <- desc2fp(apset))
```

```
An instance of a 1024 bit "FPset" with 100 molecules
```

```
> view(fpset[1])
```

```
$CMP1
An instance of "FP"
<<fingerprint>>
0 0 0 0 0 1 0 1 1 1 0 1 0 0 1 0 0 0 0 0 ... length: 1024
```

Atom Pair and Atom Pair Fingerprint Searches

The `cmp.search` function searches an atom pair database for compounds that are similar to a query compound.

```
> cmp.search(apset, apset["CMP1"], type=3, cutoff = 0.3, quiet=TRUE)
```

```
  index   cid    scores
1     1  CMP1 1.0000000
2    96 CMP96 0.3516643
3    67 CMP67 0.3117569
4    88 CMP88 0.3094629
5    15 CMP15 0.3010753
```

Compound similarity searching with *FPset*

```
> fpset1024 <- names(rev(sort(table(unlist(as(apset, "list")))))[1:1024])
> fpset <- desc2fp(apset, descnames=fpset1024, type="FPset")
> fpSim(fpset["CMP1"], fpset, method="Tanimoto", cutoff=0.2, top=6)
```

```
     CMP1     CMP96     CMP67     CMP31     CMP88     CMP15
1.0000000 0.4300000 0.3859060 0.3855856 0.3804714 0.3738602
```

Similarity Searching with PubChem Fingerprints

The fpSim function can be used for any type of binary fingerprint, here PubChem fingerprints extracted from the data block of the SDFset object.

```
> fpset <- fp2bit(sdfsample, type=3)
> fpSim(fpset[1], fpset, method="Tanimoto", cutoff=0.2, top=6)
```

```
     CMP1     CMP33     CMP98     CMP86      CMP4     CMP70
1.0000000 0.6950000 0.6763485 0.6666667 0.6448980 0.6422018
```

Pairwise comparisons are supported as well

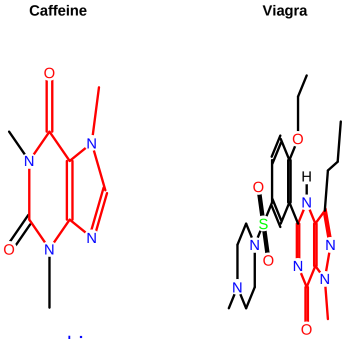
```
> fpSim(fpset[1], fpset[2])
```

```
     CMP2
0.5364807
```

Maximum Common Substructure (MCS) Searching

The *fmcsR* package provides support for identifying strict MCSs and mismatch tolerant flexible FMCSs among compounds (Wang et al., 2013).

```
> library(fmcsR); data(fmcstest) # Loads library and test sdfset object
> test <- fmcs(fmcstest[1], fmcstest[2], au=2, bu=1) # Searches for MCS with mismatc
> plotMCS(test) # Plots both query compounds with MCS in color
```



Caffeine

Viagra

FMCS-based structure similarity searching

```
> fmcsBatch(sdfset[[1]], sdfset)[1:2,]
```

```
     Query_Size Target_Size MCS_Size Tanimoto_Coefficient Overlap_Coefficient
CMP1         33          33       33            1.0000000           1.0000000
CMP2         33          26       11            0.2291667           0.4230769
```

Searching PubChem from ChemmineR

ChemmineR supports searching of the PubChem database by compound IDs or via a structure similarity search using PubChem fingerprints. The following searches PubChem by structure similarity and stores the results in an `SDFset` object.

```
> compounds <- searchSim(sdfset[1])
> compounds

An instance of "SDFset" with 10 molecules
```

Exercise V: Compound Similarity Searching

Task 1 Convert the p450 `SDFset` from Exercise I into 3 searchable descriptor databases containing: (1) atom pairs, (2) atom pair fingerprints and (3) PubChem fingerprints.

Task 2 Perform a structure similarity search against all three databases with the first compound in p450 `SDFset` as query. Compare the ranking of the three different search results.

Outline

Cheminformatics Basics

- Structure Formats
- Similarity Searching
- Physicochemical Properties

Hands-on Section

- Compound Import/Export
- Object Classes
- Compound Structure Depictions
- Compound Properties
- Compound Similarity Searching
- Compound Clustering

Binning Clustering

Compound libraries can be clustered into discrete similarity groups with the binning clustering function `cmp.cluster`.

```
> c1 <- cmp.cluster(fpset, cutoff=c(0.3, 0.6, 0.9), method="Tanimoto",
+                  quiet=TRUE)[1:8,]

sorting result...

> c1[1:8,]

   ids CLSZ_0.3 CLID_0.3 CLSZ_0.6 CLID_0.6 CLSZ_0.9 CLID_0.9
1 CMP1      100        1       91        1        1        1
2 CMP2      100        1       91        1        1        2
3 CMP3      100        1       91        1        1        3
4 CMP4      100        1       91        1        1        4
6 CMP6      100        1       91        1        1        6
7 CMP7      100        1       91        1        1        7
8 CMP8      100        1       91        1        1        8
9 CMP9      100        1       91        1        1        9

> cluster.sizestat(c1, cluster.result=2)

  cluster size      count
1           91 0.08791209
```

Jarvis-Patrick Clustering

The Jarvis-Patrick clustering algorithm is widely used in cheminformatics (Jarvis and Patrick, 1973) because it scales to very large numbers of compounds. The following performs standard Jarvis-Patrick clustering and computes the nearest neighbor table on the fly.

```
> jarvisPatrick(nearestNeighbors(fpset, numNbrs=6), k=5, mode="a1a2b")[1:20]

 CMP1   CMP2   CMP3   CMP4   CMP5   CMP6   CMP7   CMP8   CMP9  CMP10  CMP11  CMP12  CMP13  CMP14
    1      2      3      4      5      6      7      8      9     10     11     12     13     14
```

Output nearest neighbor table (*matrix*)

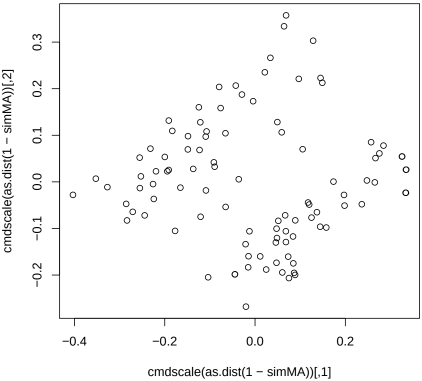
```
> nnm <- nearestNeighbors(fpset,numNbrs=6)
> nnm$similarities[1:4,]

    CMP1     CMP33     CMP98     CMP86      CMP4     CMP70
sim    1 0.6950000 0.6763485 0.6666667 0.6448980 0.6422018
sim    1 0.7823834 0.7475248 0.7348837 0.7281553 0.6666667
sim    1 0.6871795 0.6446701 0.6283186 0.6276596 0.6263158
sim    1 0.8177570 0.7348837 0.7287449 0.7136564 0.7105263
```

Multi-Dimensional Scaling (MDS)

Multidimensional scaling (MDS) algorithms start with a matrix of item-item distances and then assign coordinates for each item in a low-dimensional space to represent the distances graphically.

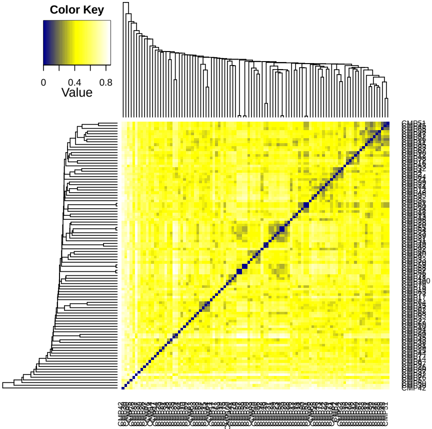
```
> simMA <- sapply(cid(fpset), function(x) fpSim(fpset[x], fpset, sorted=FALSE))
> plot(cmdscale(as.dist(1-simMA)))
```



Hierarchical Clustering

The following performs hierarchical clustering of compound structure similarities (distances). The resulting dendrogram is then plotted next to a heatmap of the corresponding similarity matrix.

```
> library(gplots)
> hc <- hclust(as.dist(1-simMA), method="single")
> heatmap.2(1-simMA, Rowv=as.dendrogram(hc), Colv=as.dendrogram(hc),
+          col=colorpanel(40, "darkblue", "yellow", "white"),
+          density.info="none", trace="none")
```



Exercise VI: Compound Clustering

Task 1 Cluster the structures in `p450 SDFset` with the binning clustering algorithm.

Task 2 Cluster the structures in `p450 SDFset` with the Jarvis-Patrick clustering algorithm.

Task 3 Cluster the structures in `p450 SDFset` with the MDS algorithm.

Task 4 Cluster the structures in `p450 SDFset` with the hierarchical clustering algorithm.

Session Information

```
> sessionInfo()

R version 3.0.2 (2013-09-25)
Platform: x86_64-unknown-linux-gnu (64-bit)

locale:
[1] C

attached base packages:
[1] stats     graphics  utils     datasets  grDevices methods   base

other attached packages:
[1] gplots_2.12.1    fmcsR_1.4.0      ChemmineR_2.14.2

loaded via a namespace (and not attached):
[1] DBI_0.2-7          KernSmooth_2.23-10 RCurl_1.95-4.1     bitops_1.0-6       caTools_1.16       digest_
```

Bibliography I

Backman, T. W., Cao, Y., Girke, T., Jul 2011. ChemMine Tools: an online service for analyzing and clustering small molecules. Nucleic Acids Res 39 (Web Server issue), 486–491.
URL `http://www.hubmed.org/display.cgi?uids=21576229`

Cao, Y., Charisi, A., Cheng, L. C., Jiang, T., Girke, T., Aug 2008. ChemmineR: a compound mining framework for R. Bioinformatics 24 (15), 1733–1734.
URL `http://www.hubmed.org/display.cgi?uids=18596077`

Chen, X., Reynolds, C. H., Nov-Dec 2002. Performance of similarity measures in 2D fragment-based similarity searching: comparison of structural descriptors and similarity coefficients. J Chem Inf Comput Sci 42 (6), 1407–1414.
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Hanser, T., Jauffret, P., Kaufmann, G., 1996. A New Algorithm for Exhaustive Ring Perception in a Molecular Graph. Journal of Chemical Information and Computer Sciences 36 (6), 1146–1152.
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URL `http://www.hubmed.org/display.cgi?uids=12767139`

Jarvis, R., Patrick, E., 1973. Clustering using a similarity measure based on shared near neighbors. IEEE Transactions on Computers 22 (11), 1025–1034.

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Wang, Y., Backman, T. W., Horan, K., Girke, T., Nov 2013. fmcsR: mismatch tolerant maximum common substructure searching in R. Bioinformatics 29 (21), 2792–2794.
URL `http://www.hubmed.org/display.cgi?uids=23962615`