

Analysis of small molecule molecular data in R

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Needs of Cheminformatics

Need to be able to search through large libraries of compounds

Requirements:

- A means of representing compound information
- An index to enable fast searching
- Algorithms to perform the search

Representing Compounds

- SDF
 - Stores a list of atoms and a connection table describing the connections between atoms
- SMILES
 - A line based format using parenthesis to represent branches in the compound structure
 - Example: CC(=O)Oc1ccccc1C(=O)O

SDF Exmple

benzene

ACD/Labs0812062058

```

6 6 0 0 0 0 0 0 0 0 0 1 V2000
  1.9050   -0.7932   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
  1.9050   -2.1232   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
  0.7531   -0.1282   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
  0.7531   -2.7882   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 -0.3987   -0.7932   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 -0.3987   -2.1232   0.0000 C   0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
2  1  1  0  0  0  0
3  1  2  0  0  0  0
4  2  2  0  0  0  0
5  3  1  0  0  0  0
6  4  1  0  0  0  0
6  5  2  0  0  0  0
M  END

```

> <Unique_ID>

XCA3464366

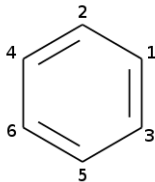
> <ClogP>

5.825

> <Molecular Weight>

499.611

\$\$\$\$



Compound Formats in ChemmineR

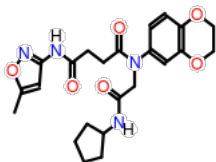
- Reading/Writing:

```
>sdfset = read.SDFset("file.sdf")  
>write.SDF(sdfset,file="output.sdf")
```
- Converting between formats (uses ChemmineOB):

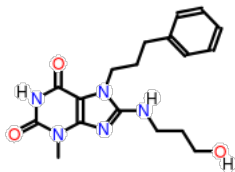
```
>convertFormatFile("CML","SDF","file.cml","file.sdf")
```
- Plotting compounds:

```
>plot(sdfset[1:2], print=FALSE)
```

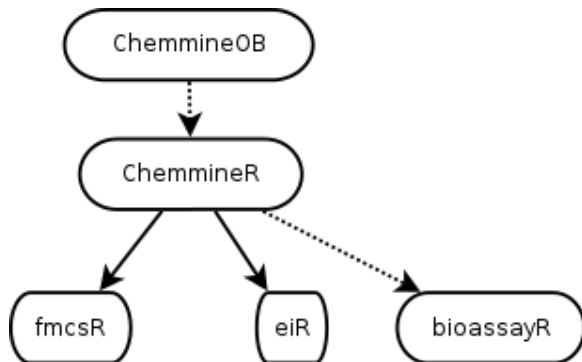
650001



650002



Tools in Bioconductor



Compound Similarity

Fundamental rule: similar compounds have similar properties

- Similarity can be defined in two ways:
 - Structural: looking at the atom connections and bond types
 - FMCS (Flexible Maximum Common Substructure): A fast and fuzzy similarity score
 - Physical: looking at various properties of the compound, such as molecular weight
 - These properties are encoded into descriptors

Compound Descriptors

- Short descriptions of certain aspects of a compound
- Fingerprints
 - Stored as a bit string
 - Each bit represents the presence or absence of a single feature
 - For example, whether or not a benzene ring is present
 - Example: 0 0 0 0 0 0 0 0 1 1 0 0 0 0 1 0 0 0 0 0 ... length: 1024
- Atom Pairs
 - A list of pairs of atoms and the shortest lengths between them
 - Example: 53822408832 53822408833 53822408834 53822408835 53822408836 ... length: 15

Indexing Compounds

- Performing some up-front work to make search faster later
- Descriptors are small enough to be indexed
- Commonly done with a similarity function
- Examples: Euclidean, Tanimoto

Computing Descriptors

Compute Atom Pairs from an SDFSet object:

```
>apset = sdf2ap(sdfset)
```

Convert that to a fingerprint:

```
>fpset = desc2fp(apset)
```

```
> fpset[[1]]
```

```
An instance of "FP" of type "unknown-5682"
```

```
<<fingerprint>>
```

```
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ... length: 1024
```

Compute Tanimoto similarity between first compound and all others:

```
>similarities = fpSim(fpset["650065"],fpset,  
                      method="Tanimoto")
```

FMCS

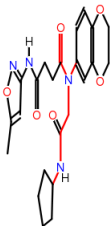
A graph-based similarity method that is defined as the largest substructure shared among two compounds

- Very sensitive and accurate search method
- Allows bond/atom mismatches
- Implemented in the fmcsR package

Caffeine



CMP1



Similarity Searching Methods

- Clustering: Compounds in the same cluster are similar to each other
- EI: A fast nearest neighbor based search method
- bioassayR: Find active compounds using screening data

Clustering

- Binning clustering
 - divide compounds into discrete similarity groups for a given set of cutoff values
- Jarvis-Patrick
 - An $O(n)$ algorithm using nearest neighbor data
- Distance matrix based methods
 - Export a distance matrix that can be used with many other types of clustering algorithms supported in R
 - Example: hierarchical clustering with *hclust*
- Implemented in the ChemmineR package

Binning

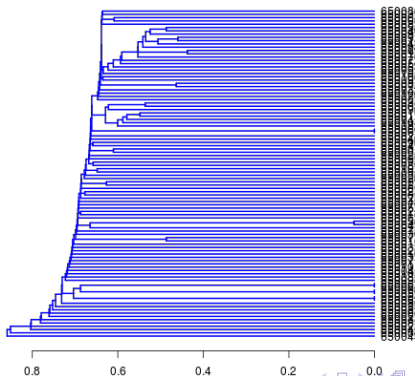
```
> clusters <- cmp.cluster(db=apset,  
                           cutoff = c(0.7, 0.8, 0.9), quiet = TRUE)  
> clusters[1:12,]  
ids CLSZ_0.7 CLID_0.7 CLSZ_0.8 CLID_0.8 CLSZ_0.9 CLID_0.9  
650049    2    48         2     48         2     48  
650050    2    48         2     48         2     48  
650059    2    54         2     54         2     54  
650060    2    54         2     54         2     54  
650061    2    56         2     56         2     56  
650062    2    56         2     56         2     56  
650063    2    58         2     58         2     58
```

Jarvis-Patrick

```
>c1 = jarvisPatrick(nearestNeighbors(apset,cutoff=0.6),  
                    k=2,mode="b")  
  
> byCluster(c1)  
$`48`  
[1] "650049" "650050"  
$`53`  
[1] "650059" "650060"  
$`54`  
[1] "650061" "650062"  
$`55`  
[1] "650063" "650064"  
$`56`  
[1] "650065" "650066"
```

Hierarchical

```
>cmp.cluster(db=apset, cutoff=0,  
  save.distances="distmat.rda", quiet=TRUE)  
>load("distmat.rda")  
>hc <- hclust(as.dist(distmat), method="single")
```



EI

- Uses precomputed compound descriptors, Atom Pair by default
- Select a small set of n exemplary compounds
- For each compound, computes the similarity to each of the n exemplars
- Embeds this n dimensional vector into k dimensional space using MDS
- Creates a nearest neighbor index using Locality Sensitive Hashing (LSH) which allows finding the nearest neighbor in near constant time
- User can then submit a query compound and find a set of similar compounds
- Query time does not scale with database size
- Implemented in the eiR package

EI Example

```
>library(eiR)
>data(sdfsampl)

#Create the database
>eiInit(sdfsampl[1:99])
>runId <- eiMakeDb(60,40)

#perform a query
>eiQuery(runId,sdfsampl[45],K=10,asSimilarity=TRUE)
```

##	query	target	similarity	target_ids
## 1	650046	650046	1.0000	245
## 2	650046	650011	0.4651	211
## 3	650046	650092	0.3923	286
## 4	650046	650004	0.1853	204
## 5	650046	650021	0.1383	220

Conclusion

- ChemmineOB
 - Provides access to the rich and fast set of functionality provided by Open Babel
- ChemmineR
 - A general cheminformatics framework
 - provides:
 - compound storage as SDF or SMILES objects
 - search algorithms
 - clustering algorithms
 - compound plotting
- eiR
 - Fast chemical search for libraries with millions of compounds
- fmcsR
 - High accuracy sub-structure based search with flexible pattern matching options
- bioassayR