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 Exmaple

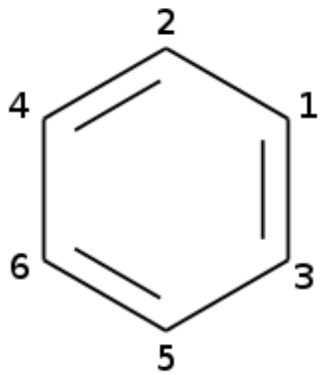
```
benzene
ACD/Labs0812062058

  6  6  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
    1.9050   -2.1232    0.0000 C   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
    0.7531   -2.7882    0.0000 C   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
   -0.3987   -2.1232    0.0000 C   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")
```

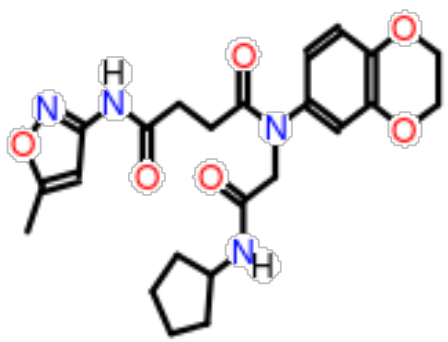
- Converting between formats (uses ChemmineOB):

```
>convertFormatFile("CML","SDF","file.cml","file.sdf")
```

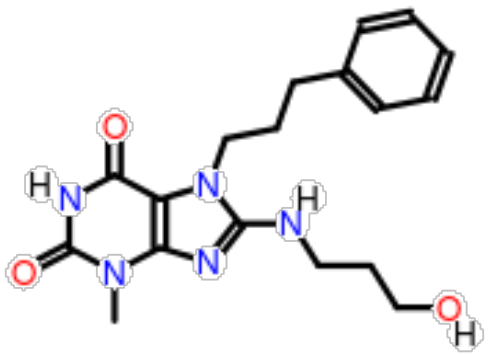
- Plotting compounds:

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

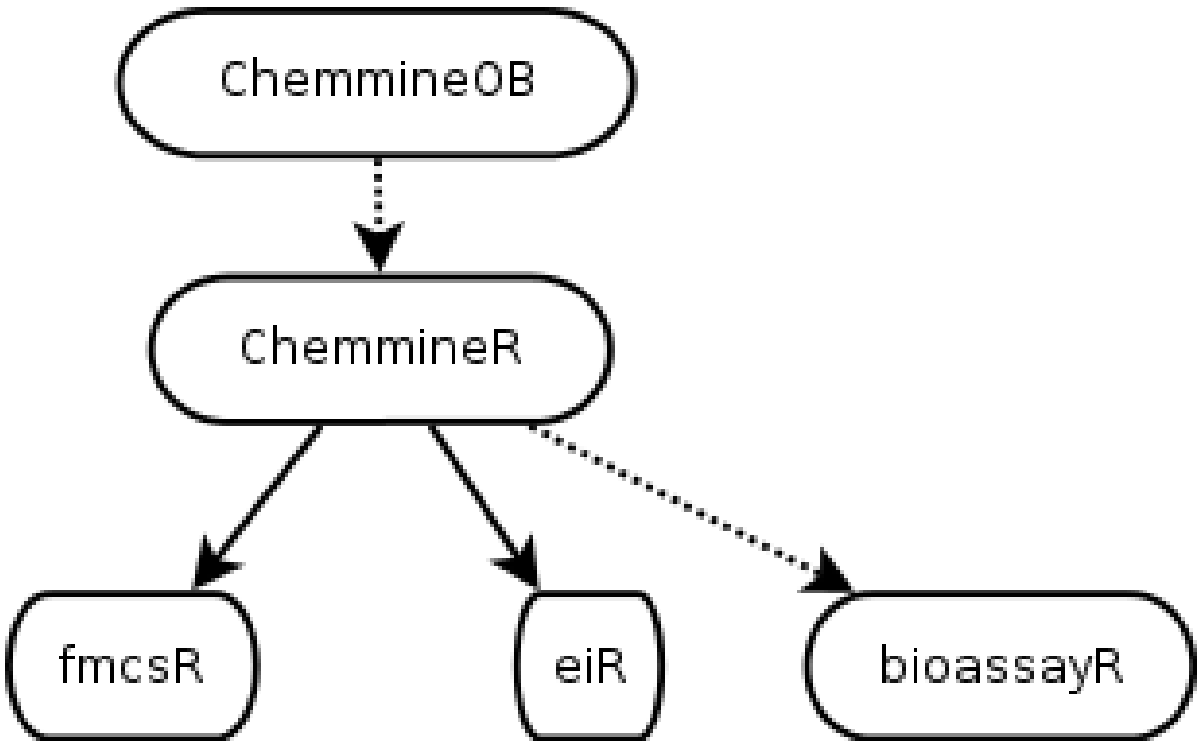
650001



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 (Flexieble 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 1 1 ... length: 1024
```

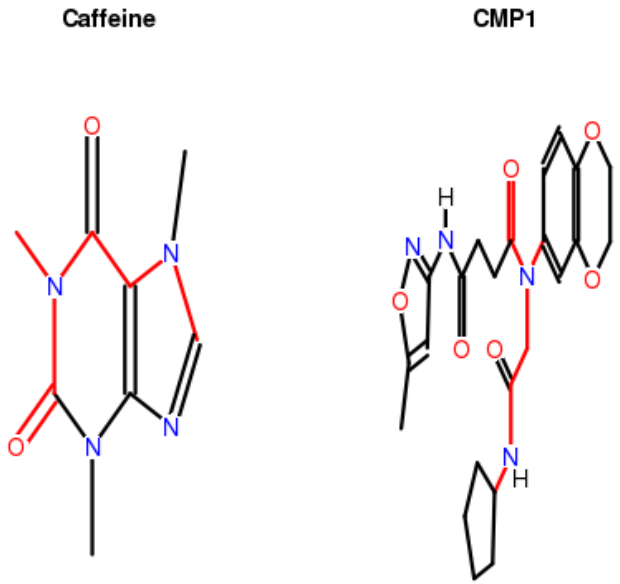
Compute Tanimoto similarity between first compound and all others:

```
>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



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 used with many other types of clustering algorithms supported in R
  - Example: hierarchical clustering with *hclust*
- Implemented in the ChemmineR package

Binning

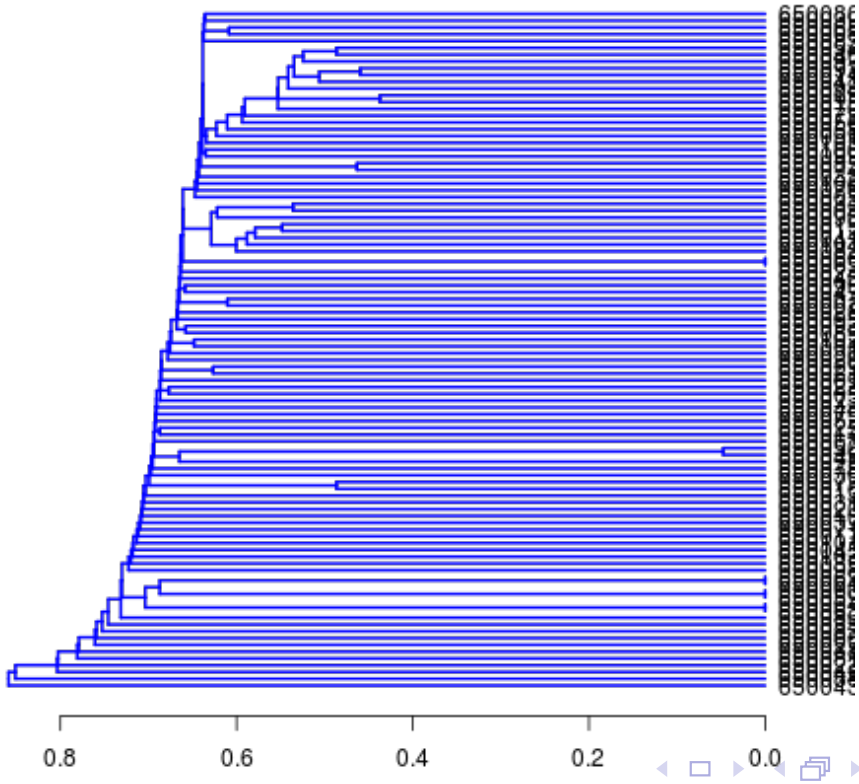
```
> clusters <- cmp.cluster(db=apset,
                          cutoff = c(0.7, 0.8, 0.9), quiet = TRUE)
> clusters[1:12,]
ids CLSZ_0.7 CLID_0.7 CLSZ_0.8 CLID_0.8 CLSZ_0.9 CLID_0.9
650049   2   48         2       48         2       48
650050   2   48         2       48         2       48
650059   2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

```
>cl = jarvisPatrick(nearestNeighbors(apset,cutoff=0.6),
                    k=2,mode="b")
> byCluster(cl)
$`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(sdfsample)

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

#peform a query
>eiQuery(runId,sdfsample[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 cheminofrmatics 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