predict-drugclass

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1 NIH.AI Workshop: Predicting Drug Function Using Small-Molecule Structure Information

1.1 Part 1: Generating Descriptor Data and Analysis

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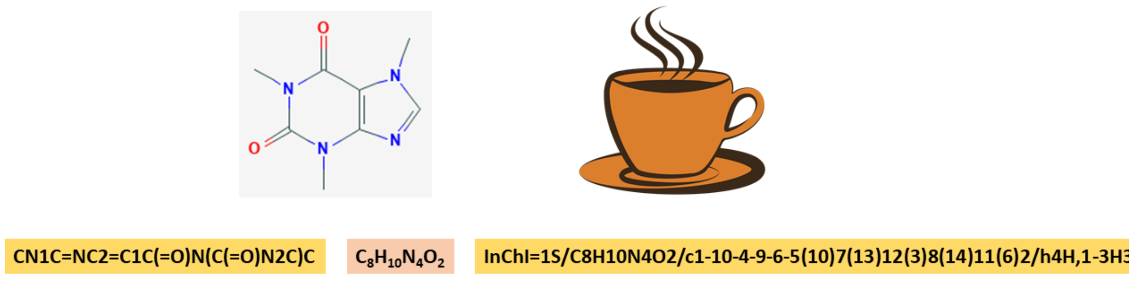
[1]:
```
from IPython.core.display import Image
Image(filename='Img/SMILES-Figures.png')
```

[1]:


O
N
N
N
N
O
CN1C=NC2=C1C(=O)N(C(=O)N2C)C
$C_8H_{10}N_4O_2$
InChI=1S/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3

1.2 Preliminary Information

Please click on this link to view the preliminary information about the workshop.

1.3 Software-setup Information

Please click on this link here to see how to install the software needed this tutorial on your own system.

1.4 Molecular/Chemical information

Please click on this link to read about the basics of molecular/chemical information (SMILES/SDF/PDB etc.). To visualize small molecules, we need atomic information. This can be obtained from different sources and formats (PubChem/DrugBank etc.; Formats: SMILES, PDB, Mol, sdf etc.). We will use SMILES strings for molecular information. There are many sources (check the last section, Supporting pages for details).

PubChem (https://pubchem.ncbi.nlm.nih.gov/) is a great resource for small molecule information. Please click on this link for a short demonstration on how to search for compounds in PubChem library.

1.5 Load the libraries

[2]:
```
import os, warnings
import numpy as np
import pandas as pd

from IPython.core.display import Image
from rdkit import Chem
from rdkit.Chem import AllChem, Draw, rdDepictor, PandasTools
from rdkit.Chem.Draw import IPythonConsole
from rdkit.Chem.Draw.MolDrawing import MolDrawing, DrawingOptions
from concurrent import futures

warnings.filterwarnings('ignore')
IPythonConsole.molSize = (450,200)
```

```
RDKit WARNING: [11:49:01] Enabling RDKit 2019.09.3 jupyter extensions
```

1.5.1 Chemoinformatics library, rdkit, for small-molecule feature generation/analysis

Go to the following link, https://www.rdkit.org/, to learn about rdkit. If you have questions about how to use I recommend you to visit a detailed version of this workshop

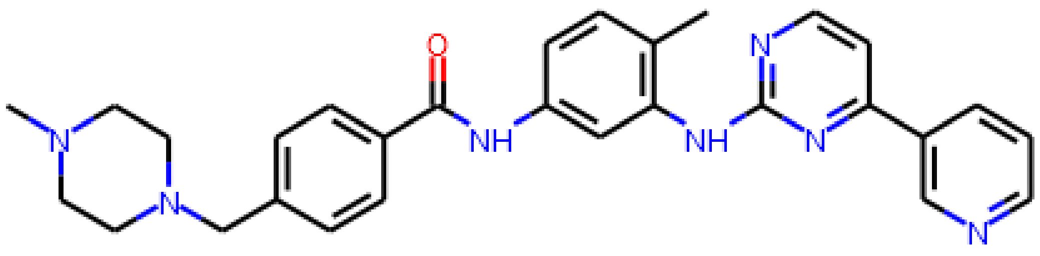
Please note that rdkit is a powerful chemoinformatics software. It can be used to read, compute (energy-minimization), visualize, create quality-figures and analyze both small molecule and protein sequences/structures. Please visit my github repo to learn about how to use rdkit for these tasks, https://github.com/ravichas/SRWkshp1

1.5.2 We can display proteins/small-molecules before computing properties

PubChem is one of the good sources for small molecule related information. You can get SMILES strings for compounds from PubChem.

[3]:
```
imatinib =␣
 ↪'CC1=C(C=C(C=C1)NC(=O)C2=CC=C(C=C2)CN3CCN(CC3)C)NC4=NC=CC(=N4)C5=CN=CC=C5'
imatinib_m = Chem.MolFromSmiles(imatinib)  #rdkit library
# generate 2D coordinates
rdDepictor.SetPreferCoordGen(True)
rdDepictor.Compute2DCoords(imatinib_m)
imatinib_m
```

[3]:



```
[4]: import py3Dmol

     # The crystal structure of COVID-19 main protease in complex with an inhibitor␣
      ↪N3
     # The main protease (enzyme that catalyses/cuts proteins into smaller␣
      ↪fragments) of coronavirus makes most of these cuts. The one shown here
     # (PDB entry 6lu7) is from the SARS-CoV-2 (or 2019-nCoV) coronavirus that is␣
      ↪currently posing dangers in Wuhan

     view = py3Dmol.view(query='pdb:6lu7')
     view.setStyle({'cartoon':{'color':'spectrum'}})
```

```
[4]: <py3Dmol.view at 0x20fbae6a820>
```

1.6 Generating molecular properties

For this section, we will be using cdkit and Mordred (a molecular descriptor calculator) to generate molecular descriptors. Follow the links shown below for information on mordred calculator:

- https://jcheminf.biomedcentral.com/articles/10.1186/s13321-018-0258-y
- https://github.com/mordred-descriptor/mordred

1.7 Molecular fingerprints

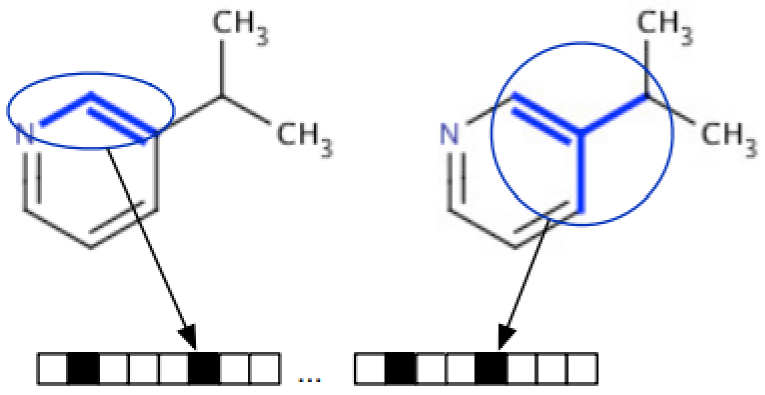
``Molecular fingerprints are a way of encoding the structure of a molecule. The most common type of fingerprint is a series of binary digits (bits) that represent the presence or absence of particular substructures in the molecule.'' (quote from OpenBabel documentation)

We will use Morgan Fringerprints. You can read about the details here, https://www.ncbi.nlm.nih.gov/pubmed/20426451 and here, https://www.daylight.com/dayhtml/doc/theory/theory.finger.html

Note most of the ideas are based on examples from cdkit manual. In a nutshell, each fragment in a molecule correspond to a bit. Two similar molecular fingerprints will have many common bits.

[5]:
```python
Image(filename='Img/FPComp.PNG',width = 300, height = 300 )
# (Following figure is based on an an online presentation)
```

[5]:

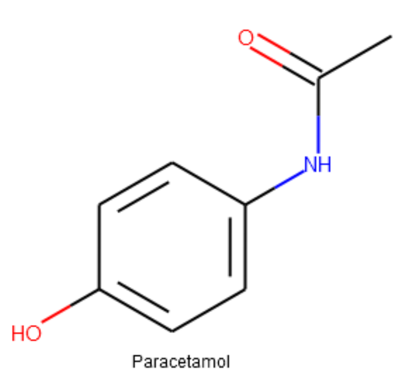


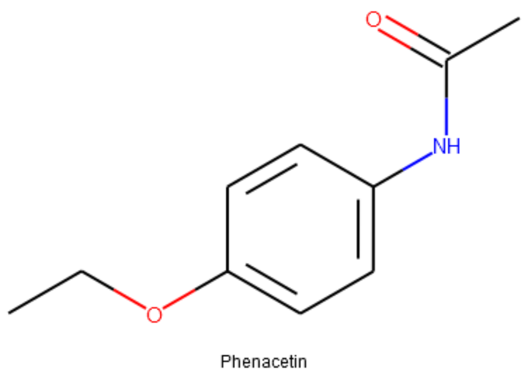
We are going to use fingerprint as features that define molecule. To explain the idea, let us use the two pain-killer drugs, paracetamol and pheacetin (withdrawn) as an example. First let us visualize, compute and analyze both the molecule and its fingerprint.

[6]:
```python
IPythonConsole.molSize = (450,200)

# fever reducer
paracetamol = 'CC(=O)NC1=CC=C(O)C=C1'
paracetamol_m = Chem.MolFromSmiles(paracetamol)
rdDepictor.Compute2DCoords(paracetamol_m)

# withdrawn fever reducer
phenacetin = 'CCOC1=CC=C(NC(C)=O)C=C1'
phenacetin_m = Chem.MolFromSmiles(phenacetin)
rdDepictor.Compute2DCoords(phenacetin_m)

# save the molecules as a list
mols = [paracetamol_m, phenacetin_m]
```

[7]:
```python
Draw.MolsToGridImage(mols, subImgSize=(400, 300), molsPerRow = 2, legends =␣
↪['Paracetamol','Phenacetin'])
```

[7]:





1.7.1 We can convert fingerprint to bits and view them

[8]:
```python
# instantiate a dictionary
bi1 = {}

fp1 = AllChem.GetMorganFingerprintAsBitVect(paracetamol_m, radius=2,␣
↪bitInfo=bi1)
bits1 = fp1.ToBitString()
print(len(bits1))
bits1
```

```
2048
```

[8]:
```
'0000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000100000000000000000000000000000000000000000000000
00000010000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000010000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000100000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000100000000000000000000000000000000000000000000000000000
00000000100000000000000000000000000000000000100000100000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000001000000000000000000000
00000000000000000010000000000000000000100000000000000000000000000000000000000000
00000000000000000000000000000000010000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000001000000000000000000000000000000000000000000000
00000000000000000000010000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000000000000
```

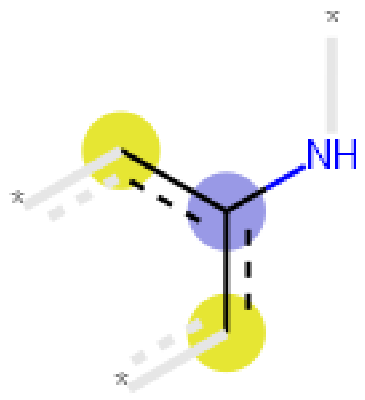
```
00000000000000000000000000000000000000000000000000000000000000000000000000000000
00010000000000000000000000000000000000000000000000000000000000000000000000000000
00000000000000000000000000000000000000000000000000000000000000000000000100000000
00000000000000000001000000000000000000000000000000000000010000000000000000000000
00000000000000000000000000000000001000000000000000000000000000000000000000000010
00000000000000000000000000000000000000000000000000000000000000000000000000000000
0000000000000000000000000000000000000000000000000'
```

[9]:
```
print(len(list(fp1.GetOnBits())))
print(list(fp1.GetOnBits()) )
```

```
20
[191, 245, 530, 650, 745, 807, 843, 849, 1017, 1057, 1077, 1152, 1313, 1380,
1602, 1750, 1778, 1816, 1873, 1917]
```

[10]:
```
# In its simplest form, the new code lets you display the atomic environment␣
↪that sets a particular bit. Here we will look at bit 589:
Draw.DrawMorganBit(paracetamol_m,191,bi1)
```

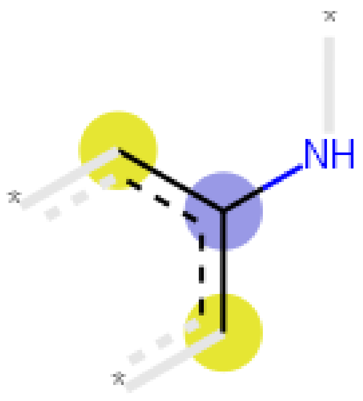
[10]:



Let us check whether Phencetin have the same fragment?

[11]:
```
bi2 = {}
fp2 = AllChem.GetMorganFingerprintAsBitVect(phenacetin_m, radius=2, bitInfo=bi2)
bits2 = fp2.ToBitString()
# In its simplest form, the new code lets you display the atomic environment␣
↪that sets a particular bit. Here we will look at bit 589:
Draw.DrawMorganBit(phenacetin_m,191,bi2)
```

[11]:



```
[12]: # Let us find common bits based on Dr. Jan Jensen's tutorial
      # you use set operation by saving the result not as a list
      common_bits = set( fp1.GetOnBits()) & set(fp2.GetOnBits())
      combined_bits = set( fp1.GetOnBits()) | set(fp2.GetOnBits())
```

```
[13]: print('Common_bits between Paracetamol and Phenacetin: ', common_bits,'\n')
      print('Combined_bits between Paracetamol and Phenacetin: ', combined_bits)
```

```
Common_bits between Paracetamol and Phenacetin:  {1152, 1057, 1380, 807, 650,
843, 849, 530, 1873, 1077, 1750, 245, 1816, 1017, 1917, 191}

Combined_bits between Paracetamol and Phenacetin:  {1152, 650, 530, 1816, 1057,
1313, 294, 807, 1452, 1077, 695, 191, 1602, 322, 69, 843, 718, 80, 849, 1873,
1750, 1238, 1380, 102, 745, 237, 1778, 245, 1017, 1917}
```

1.7.2 2D similarity

$$\text{Tanimoto} = \frac{N_{AB}}{N_A + N_B - N_{AB}}$$

For 3D functionality in the RDKit, refer to this link, http://rdkit.org/docs_temp/Cookbook.html
For today, we are going to stay with 2D fingerprints.

```
[14]: # this will give the common bits and the proportion will tell us the similarity
      print('Raw Calculation :', len(common_bits)/len(combined_bits),'\n')

      # import the library
      from rdkit import DataStructs

      # Tanimoto Similarity
      print('Tanimoto Similarity: ', DataStructs.TanimotoSimilarity(fp1, fp2))
```

```
Raw Calculation : 0.5333333333333333

Tanimoto Similarity:  0.5333333333333333
```

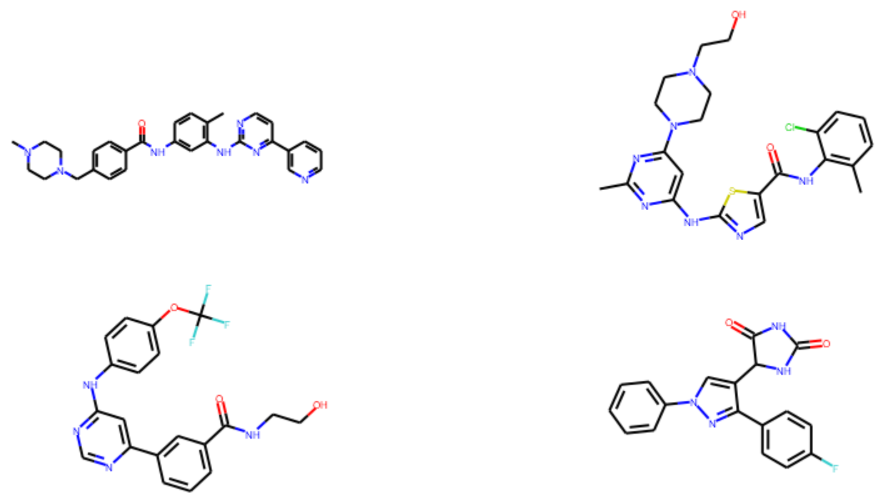
1.8 Mordred: For computing descriptors

We will be using a python package called mordred for generating descriptors.
Mordred Github Page: https://github.com/mordred-descriptor/mordred
and click here to see the complete list of mordred descriptors,
https://mordred-descriptor.github.io/documentation/master/descriptors.html

1.8.1 Compute molecular descriptors for a library of small-molecules

[15]:
```
from rdkit import Chem
from mordred import Calculator, descriptors

# create descriptor calculator with all descriptors
calc = Calculator(descriptors, ignore_3D=True)

IPythonConsole.molSize = (450,400)
dasatinib = 'CC1=C(C(=CC=C1)Cl)NC(=O)C2=CN=C(S2)NC3=CC(=NC(=N3)C)N4CCN(CC4)CCO'
dasatinib_m = Chem.MolFromSmiles(dasatinib)
gnf5 = 'C1=CC(=CC(=C1)C(=O)NCCO)C2=CC(=NC=N2)NC3=CC=C(C=C3)OC(F)(F)F'
gnf5_m = Chem.MolFromSmiles(gnf5)
dph = 'C1=CC=C(C=C1)N2C=C(C(=N2)C3=CC=C(C=C3)F)C4C(=O)NC(=O)N4'
dph_m = Chem.MolFromSmiles(dph)

molecules = [ imatinib_m, dasatinib_m, gnf5_m, dph_m ]
Draw.MolsToGridImage(molecules, molsPerRow = 2, subImgSize=(450, 200))
```

[15]:



Please inspect the descriptor table before you use them in other calculations.
Especially when you are generating all the descriptors, some of the columns may contain NA or Nan etc.

[16]:
```
# calculate multiple molecule
mols = [Chem.MolFromSmiles(smi) for smi in [imatinib, dasatinib, gnf5, dph]]

# as pandas
df = calc.pandas(mols)
```

```
100%|      | 4/4 [00:02<00:00,  1.87it/s]
```

[17]:
```
df
```

[17]:
```
         ABC      ABCGG  nAcid  nBase    SpAbs_A   SpMax_A  SpDiam_A  \
0  29.198227  19.516970      0      2  49.161634  2.372244  4.744487
1  25.731643  19.151718      0      1  42.312870  2.394767  4.762938
2  23.132682  16.941805      0      0  38.063201  2.370962  4.741923
3  19.924959  16.140292      0      0  32.867760  2.498596  4.828813

      SpAD_A   SpMAD_A  LogEE_A  …      SRW10     TSRW10          MW  \
0  49.161634  1.328693  4.541483  …  10.415502  73.587263  493.259009
1  42.312870  1.282208  4.422390  …  10.323283  82.603238  487.155722
2  38.063201  1.268773  4.312334  …  10.143881  65.313648  418.125275
3  32.867760  1.314710  4.170130  …  10.150621  75.953704  336.102254

        AMW  WPath  WPol  Zagreb1  Zagreb2   mZagreb1  mZagreb2
0  7.253809   5324    56    194.0    224.0   9.972222  8.083333
1  8.256877   3723    50    172.0    200.0  10.472222  7.277778
2  8.896282   2918    42    152.0    171.0  10.090278  6.597222
3  8.844796   1431    38    136.0    162.0   7.250000  5.388889

[4 rows x 1613 columns]
```

Please visit GitHub repository to see additional examples and take-home exercises.

1.9 Part 2: Machine Learning for Predicing Drug Function Using Molecular Structures

Please check out a detailed version of this project from https://github.com/ravichas/SRWkshp1a

1.10 Preliminary Information

We will use the following manuscript as a testcase to explain the Machine-Learning concepts:

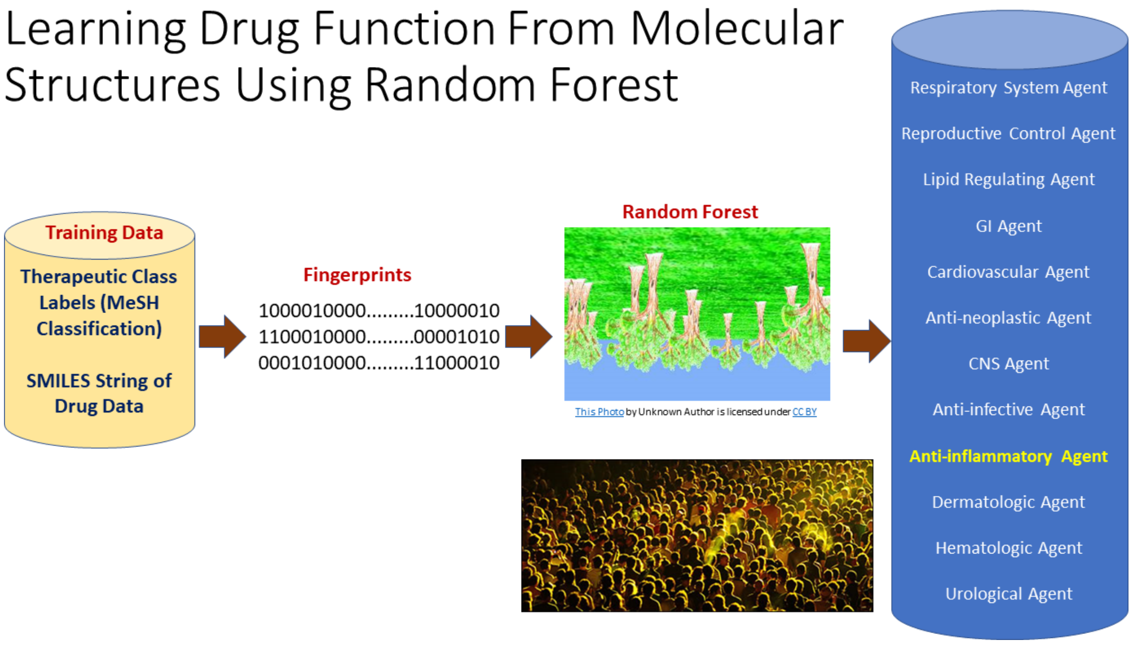
https://www.ncbi.nlm.nih.gov/pubmed/31518132

Overview of the work: * Chemical structures with MeSH derived therapeutic drug classes are the inputs. * **Random Forest (RF)** Machine-Learning (ML) method and **Convolution Neural Network** was used for classification. For this workshop, we fill focus on RF for this workshop.

1.10.1 Here is a schematic overview of the modeling procedure

[18]:
```
from IPython.display import Image
Image('Img/DrugFunctionModeling-banner.png', width=900, height=900)
```

[18]:



1.10.2 To create drug function classifier models, we need two things:

- Chemical structures and their associated class labels
- Descriptors (Fingerprints)

Input dataset can be constructed using PubChem (https://pubchem.ncbi.nlm.nih.gov/). You can check my Github repository for details, https://github.com/ravichas/SRWkshp1a (section 4 on the ML-UsingSmallMoleculeData.ipynb)

[19]:
```
## Preliminary library setup
import os, random, time, numpy as np
import matplotlib.pyplot as plt
from collections import Counter
from rdkit import Chem, DataStructs
from rdkit.Chem import Draw
from sklearn import preprocessing
from sklearn.ensemble import RandomForestClassifier
```

1.11 Load the data

[20]:
```
import pandas as pd
df3  = pd.read_csv('Data/3cls_rmsaltol.csv')

# five class dataset
df5  = pd.read_csv('Data/5cls_rmsaltol.csv')

print("Here are few first/last 5 lines of the df3 data")
df3.iloc[0:6, [1,2]]
```

```
Here are few first/last 5 lines of the df3 data
```

[20]:
```
  class                                             smiles
0   cns                                         O=C1CC=CO1
1   cns      CCC(=O)O[C@@]1(c2ccccc2)C[C@H](C)N(C)C[C@H]1C
2   cns                                     C=CCC(N)C(=O)O
3   cns   CC[C@@]12CCN(CC3CC3)[C@@H](C(=O)c3ccc(O)cc31)C2C
4   cns                           c1csc(C2(N3CCCCC3)CCCCC2)c1
5   cns                          O=C([O-])/C=C1\CCCc2ccccc2C1O
```

1.11.1 Explore the dataset

[21]:
```
# All the data
print('Dimension of 3-class dataset', df3.shape)
print('Dimension of 5-class dataset', df5.shape)
# print('Dimension of 12-class dataset', df12.shape, '\n')
```

```
Dimension of 3-class dataset (3104, 3)
Dimension of 5-class dataset (5760, 3)
```

Assign a specific dataset for modeling/analysis? For choosing a 3-class data, use df = df3

For choosing a 5-class data, use df = df5

For now, we are going to use 3-class data for modeling.

[22]:
```
## Assign a dataset for analysis
df = df3
```

1.12 Prepare the data for modeling

Encode target labels with value between 0 and n_classes-1.

[23]:
```
x = df['smiles'].values

mols1 = [Chem.MolFromSmiles(smi) for smi in x]
outcome = df['class'].values
```

```
le = preprocessing.LabelEncoder()
le.fit(outcome);
print('What labels are available in classes?:', list(le.classes_))
ys_fit = le.transform(outcome)

print('transformed outcome:  ', ys_fit)
```

```
What labels are available in classes?: ['antineoplastic', 'cardio', 'cns']
transformed outcome:   [2 2 2 … 1 1 1]
```

From the above analysis, for a 3-class, df3a data, we see that

0: Antineoplastic Agents (antineoplastic)
1: Cardiovascular Agents (cardio)
2: Central Nervous System Agents (cns)

1.13 Data Analysis

Let us answer the following questions:

- How many Classes/Samples?
- Is this a balanced outcome data?

[24]:
```
bin_count = np.bincount(ys_fit)
n_classes = len(bin_count)
print('How many classes? ',n_classes)
print('How many samples? ', len(ys_fit) )

print('How many from each class (raw numbers)? ', bin_count )
print('How many from each class (proportions)?: ', bin_count/(sum(bin_count)))
```

```
How many classes?  3
How many samples?  3104
How many from each class (raw numbers)?  [1177  788 1139]
How many from each class (proportions)?:  [0.37918814 0.25386598 0.36694588]
```

1.14 Generate fingeprints:

Read the following paper for details, https://www.ncbi.nlm.nih.gov/pubmed/20426451

[25]:
```
# Time to generate the Fingerprints: 8.323498249053955 seconds on core i7 laptop

time_start = time.time()

from rdkit.Chem import AllChem
fp1 = [AllChem.GetMorganFingerprintAsBitVect(m, 2, nBits=1024) for m in mols1]

# convert RDKit explicit vectors into NUMPY array
np_fps = np.asarray(fp1)
```

```
time_elapsed = time.time()-time_start
txt = 'Time to generate the Fingerprints: {} seconds '
print(txt.format(time_elapsed))
```

```
Time to generate the Fingerprints: 5.567084550857544 seconds
```

1.14.1 Let us display the first 11 columns of the top 20 molecular fingerprints

[26]:
```
print(np_fps[0:10,0:20])
```

```
[[0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 1 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0]
 [0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 0 1 0 1 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0]
 [0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0]
 [0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0]
 [0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0]]
```

1.15 Getting ready to do modeling

First, let us split the data

[27]:
```
from sklearn.model_selection import train_test_split
seed = 123

train_X, test_X, train_y, test_y = train_test_split(np_fps, ys_fit,
                                                    train_size=0.75,
                                                    test_size=0.25,
                                                    random_state=seed,
                                                    stratify = ys_fit)
train_y = list(train_y)
test_y = list(test_y)
```

1.15.1 Explore the proportion of outcomes to answer questions about data imbalance

[28]:
```
# Even outcome for this class
np.bincount(ys_fit)/len(ys_fit)
```

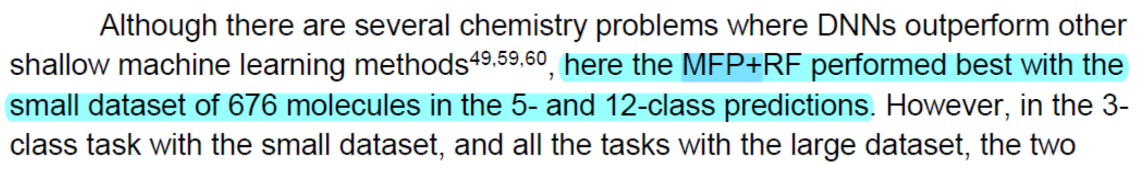
[28]:
```
array([0.37918814, 0.25386598, 0.36694588])
```

1.16 Supervised Learning using Random Forest

We will use Random-Forest based classifier for classification. #### Why we are focussing on Random Forest?

[29]:
```
Image('Img/PaperSummary1.png')
```

[29]:



Although there are several chemistry problems where DNNs outperform other shallow machine learning methods[49,59,60], here the MFP+RF performed best with the small dataset of 676 molecules in the 5- and 12-class predictions. However, in the 3-class task with the small dataset, and all the tasks with the large dataset, the two

[30]:
```
# get a random forest classifiert with 100 trees
seed = 1123
rf = RandomForestClassifier(n_estimators=50, random_state=seed)
```

[31]:
```
from pprint import pprint
# View the parameters of the random forest
print('Parameters will be used for this model:\n')
pprint(rf.get_params())
```

```
Parameters will be used for this model:

{'bootstrap': True,
 'ccp_alpha': 0.0,
 'class_weight': None,
 'criterion': 'gini',
 'max_depth': None,
 'max_features': 'auto',
 'max_leaf_nodes': None,
 'max_samples': None,
 'min_impurity_decrease': 0.0,
 'min_impurity_split': None,
 'min_samples_leaf': 1,
 'min_samples_split': 2,
 'min_weight_fraction_leaf': 0.0,
 'n_estimators': 50,
 'n_jobs': None,
 'oob_score': False,
 'random_state': 1123,
 'verbose': 0,
 'warm_start': False}
```

[32]:
```
# train the random forest
rf.fit(train_X, train_y);
```

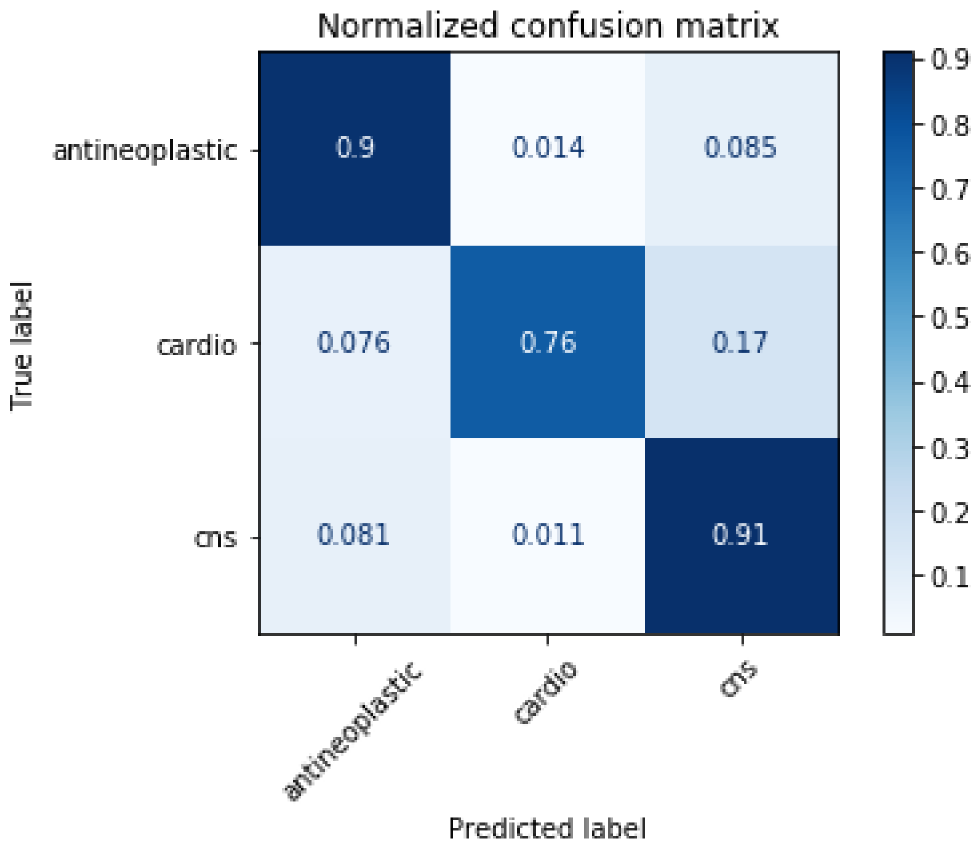
[33]:
```
from sklearn import metrics
from sklearn.metrics import balanced_accuracy_score

pred_y = rf.predict(test_X)
```

```
acc = metrics.accuracy_score(test_y, pred_y)
print("Test set accuracy: {:.2f}".format(acc))

balanced_acc_score = balanced_accuracy_score(test_y, pred_y)
print("Balanced set Accuracy Score: {:.2f}".format(balanced_acc_score))
```

```
Test set accuracy: 0.87
Balanced set Accuracy Score: 0.86
```

[34]:
```
# Plot non-normalized confusion matrix
# get a random forest classifiert with 100 trees
np.set_printoptions(precision=3)
from sklearn.metrics import plot_confusion_matrix

titles_options = [("Normalized confusion matrix", 'true')]

for title, normalize in titles_options:
    disp = plot_confusion_matrix(rf, test_X, test_y,
                                 display_labels=le.classes_,
                                 cmap=plt.cm.Blues,
                                 normalize=normalize)
    disp.ax_.set_title(title)
    plt.xticks(rotation=45)

    print(title)
    print(disp.confusion_matrix)

plt.show()
```

```
Normalized confusion matrix
[[0.901 0.014 0.085]
 [0.076 0.756 0.168]
 [0.081 0.011 0.909]]
```



1.17 Inference

0: Antineoplastic Agents (antineoplastic)
1: Cardiovascular Agents (cardio)
2: Central Nervous System Agents (cns)

[35]:
```
print(rf.predict(test_X[10:13]))
print(test_y[10:13])
# pred_y = rf_best_grid.predict(test_X)
```

```
[0 1 0]
[0, 1, 0]
```

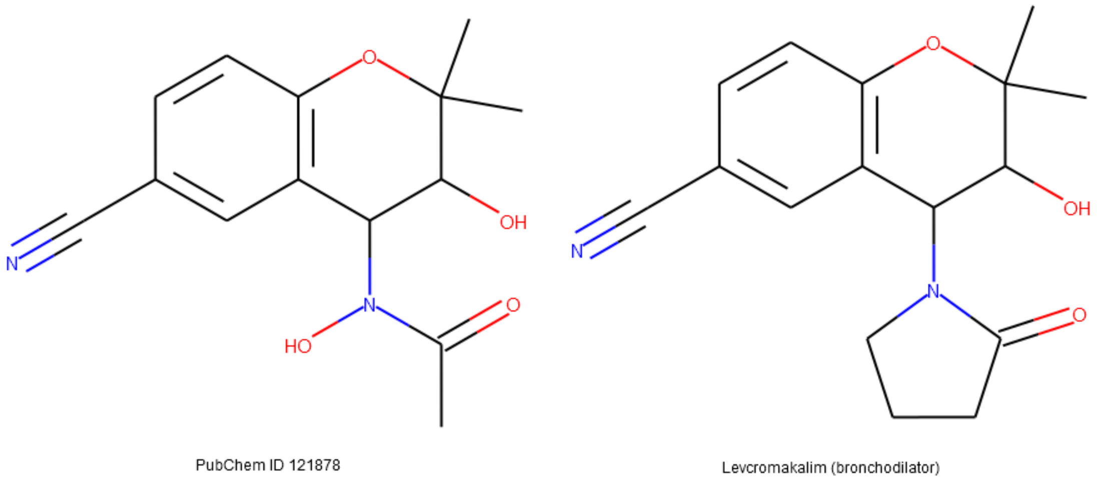
1.18 Questions

- Can molecular fingerprints inherently capture molecular chemical features (Ex. Mol Wt., # of Hydrogen Bond Donors, # of Hydrogen Bond Acceptors)?
- Few drugs have similar fingerprints for CNS and Cardio class. What functional groups/fragments in the misclassified compounds are common?
- What about 3D features?

1.18.1 In the paper, https://pubmed.ncbi.nlm.nih.gov/31518132/, the Authors using the 5-label dataset had identified drugs that were misclassified and upon inspection seems to have structures similar to that of the misclassified class.

[36]:
```
# misclassified as a respiratory system drug
cid_121878 = 'CC(=O)N(C1C(C(OC2=C1C=C(C=C2)C#N)(C)C)O)O'
cid_121878_m = Chem.MolFromSmiles(cid_121878)

rdDepictor.SetPreferCoordGen(True)
rdDepictor.Compute2DCoords(cid_121878_m)
# similarity with bronchodilator molecule
cid_93504 = 'CC1(C(C(C2=C(O1)C=CC(=C2)C#N)N3CCCC3=O)O)C'
cid_93504_m = Chem.MolFromSmiles(cid_93504)
rdDepictor.Compute2DCoords(cid_93504_m)


molecules = [ cid_121878_m, cid_93504_m ]
Draw.MolsToGridImage(molecules, molsPerRow = 2,
                     subImgSize=(450, 450),
                     legends = ['PubChem ID 121878', 'Levcromakalim␣
↪(bronchodilator)'])
```

[36]:



1.19 Final thoughts and questions to ponder!

- Can the model misclassification be due to lack of training and nothing to do with repurposing?
- What about bioactive conformations?

1.20 How can we improve the models?

There are several parametes (number of estimators, maximum features etc.) that could be assigned different values. These parameters are commonly referred to as Hyperparameters. Choosing the right combination is called HyperParameter Optimization (HPO).

1.21 Hyperparameter values (HP) and HP Optimization (HPO)

For ScikitLearn implementation of RandomForest, we can adjust several HP values. Here is the complete list:

```
{'bootstrap': True,
 'ccp_alpha': 0.0,
 'class_weight': None,
 'criterion': 'gini',
 'max_depth': None,
 'max_features': 'auto',
 'max_leaf_nodes': None,
 'max_samples': None,
 'min_impurity_decrease': 0.0,
 'min_impurity_split': None,
 'min_samples_leaf': 1,
 'min_samples_split': 2,
 'min_weight_fraction_leaf': 0.0,
 'n_estimators': 50,
 'n_jobs': None,
 'oob_score': False,
 'random_state': 1123,
 'verbose': 0,
 'warm_start': False}
```

Where do we start? The best option is to read the documentation, https://scikit-learn.org/stable/modules/generated/sklearn.ensemble.RandomForestClassifier.html We have adopted the following choices based on the manuscript.

Parameter	Values
n_estimators	50, 250, 1000, 4000, 8000, 16000
max_features	sqrt, log2
min_samples_leaf	1, 10, 100, 1000
class_weight	None, balanced_subsample, balanced

A HPO RandomizedSearchCV run was carried out in NIH HPC with the list shown in the table and found the following best combination.

Parameter	Values
n_estimators	8000
max_features	log2

Parameter	Values
min_samples_leaf	1
class_weight	balanced

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