Lecture 14: Biophysical Modeling

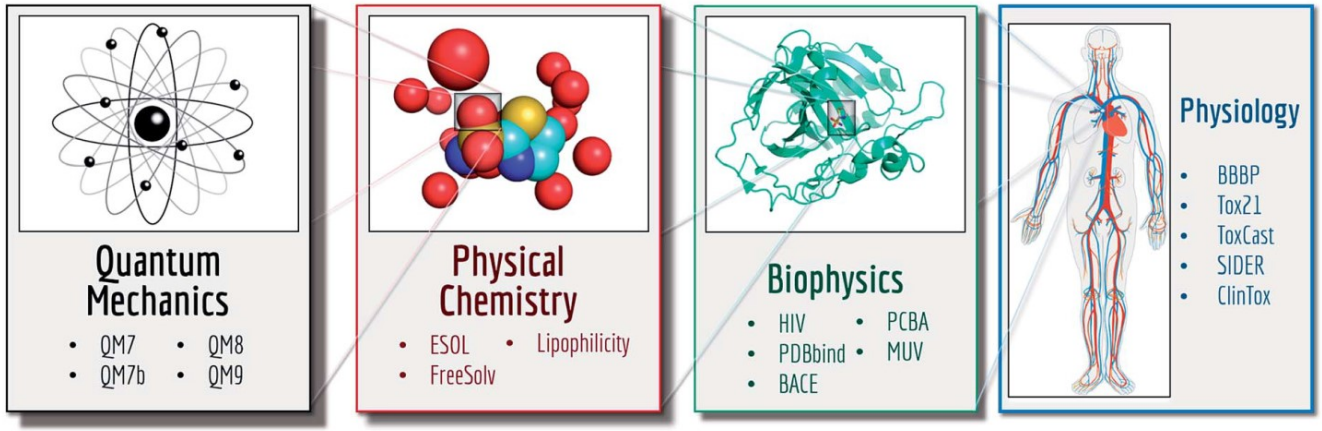
Credit

Slides are partially based on the material in Ramsundar, Bharath; Eastman, Peter; Walters, Patrick; Pande, Vijay. Deep Learning for the Life Sciences, Chapter 5.

https://medium.com/@stefan.schroedl/machine-learning-for-drug-discovery-in-a-nutshell-part-ii-24f90d5963d9

MoleculeNet

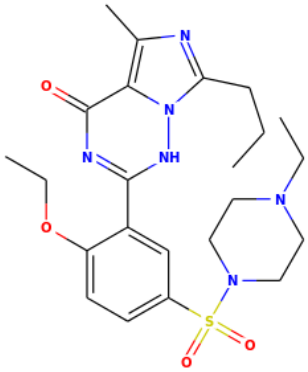
- A large set of dataset useful for molecular machine learning, included with DeepChem.
- Data from over 70,000 compounds
- Integrated with DeepChem package



Wu, Zhenqin, Bharath Ramsundar, Evan N. Feinberg, Joseph Gomes, Caleb Geniesse, Aneesh S. Pappu, Karl Leswing, and Vijay Pande. "MoleculeNet: a benchmark for molecular machine learning." Chemical science 9, no. 2 (2018): 513-530.

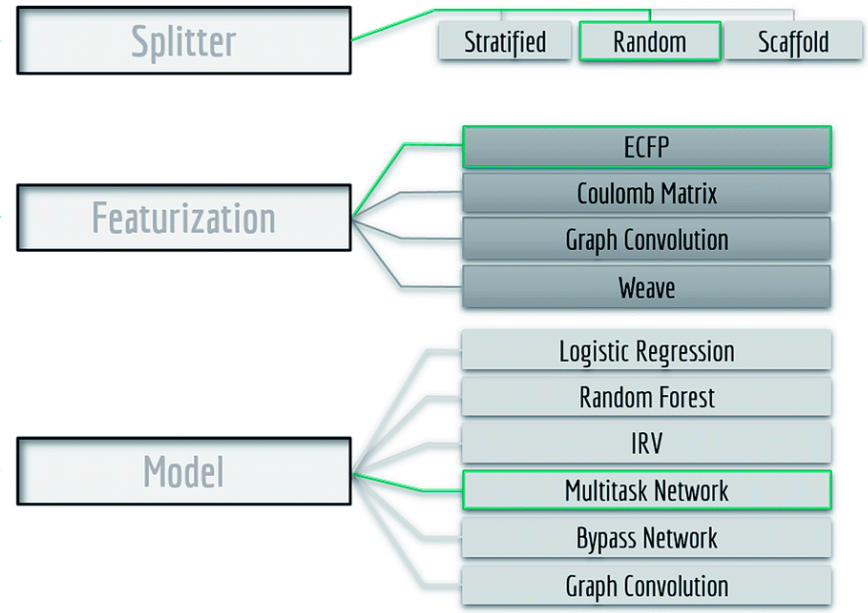
RDKit

- RdKit is a popular Cheminformatics Python library for computing features and molecular representation.



Coding using DeepChem

```python
"""
Script that trains multitask models on Tox21 dataset.
"""
from __future__ import print_function
from __future__ import division
from __future__ import unicode_literals

import numpy as np
import deepchem as dc

np.random.seed(123)

# Load Tox21 dataset
n_features = 1024
tox21_tasks, tox21_datasets, transformers = dc.molnet.load_tox21(split="random",
                                                                  featurizer="ECFP")

train_dataset, valid_dataset, test_dataset = tox21_datasets

# Define metric
metric = dc.metrics.Metric(dc.metrics.roc_auc_score, np.mean)
# Define model
model = dc.models.TensorflowMultiTaskClassifier(
    len(tox21_tasks), n_features, layer_sizes=[1000], dropouts=[.25],
    learning_rate=0.001, batch_size=50)

# Fit trained model
model.fit(train_dataset)
model.save()

print("Evaluating model")
train_scores = model.evaluate(train_dataset, [metric], transformers)
valid_scores = model.evaluate(valid_dataset, [metric], transformers)

print("Train scores")
print(train_scores)

print("Validation scores")
print(valid_scores)
```



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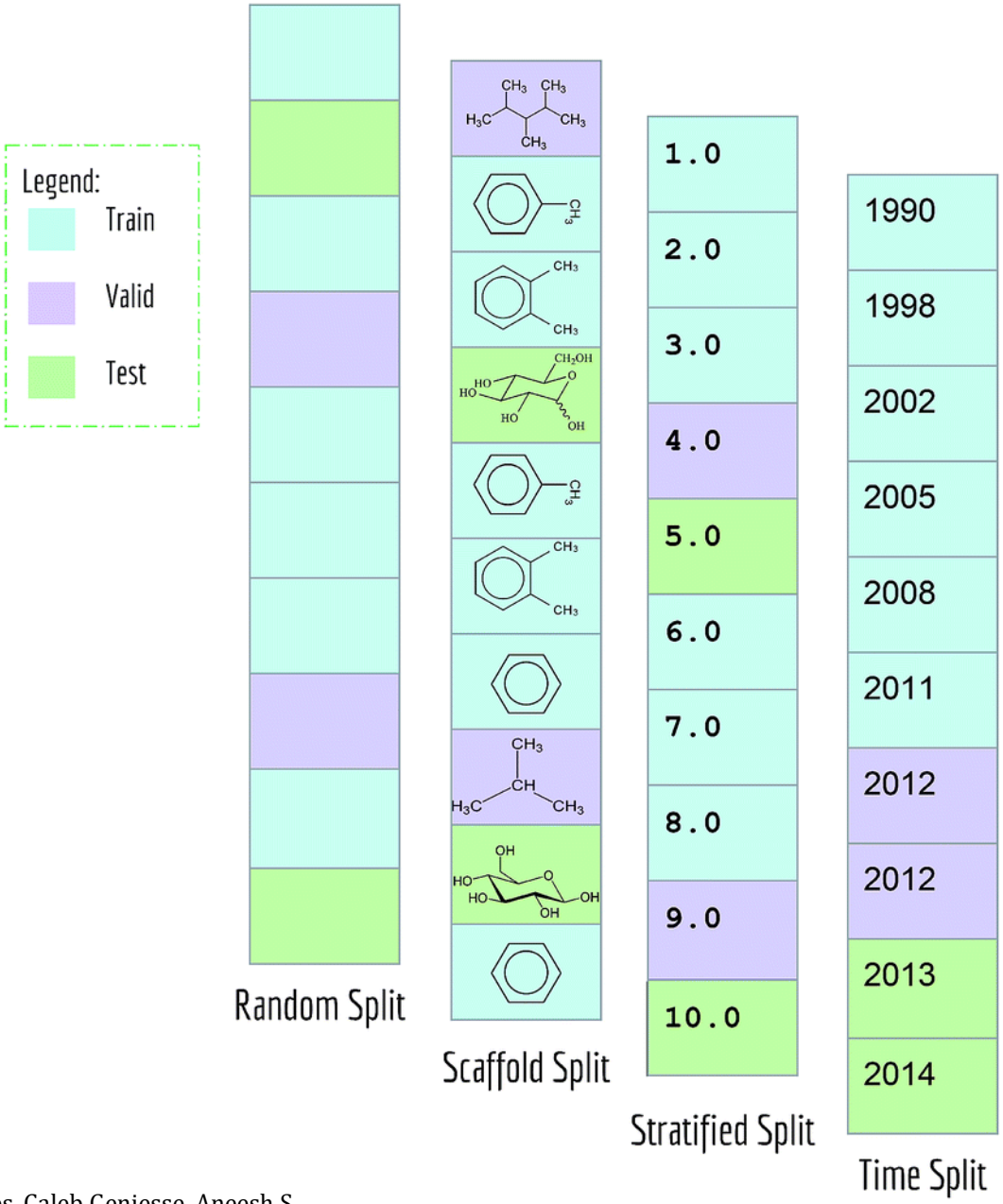
Splitting Method



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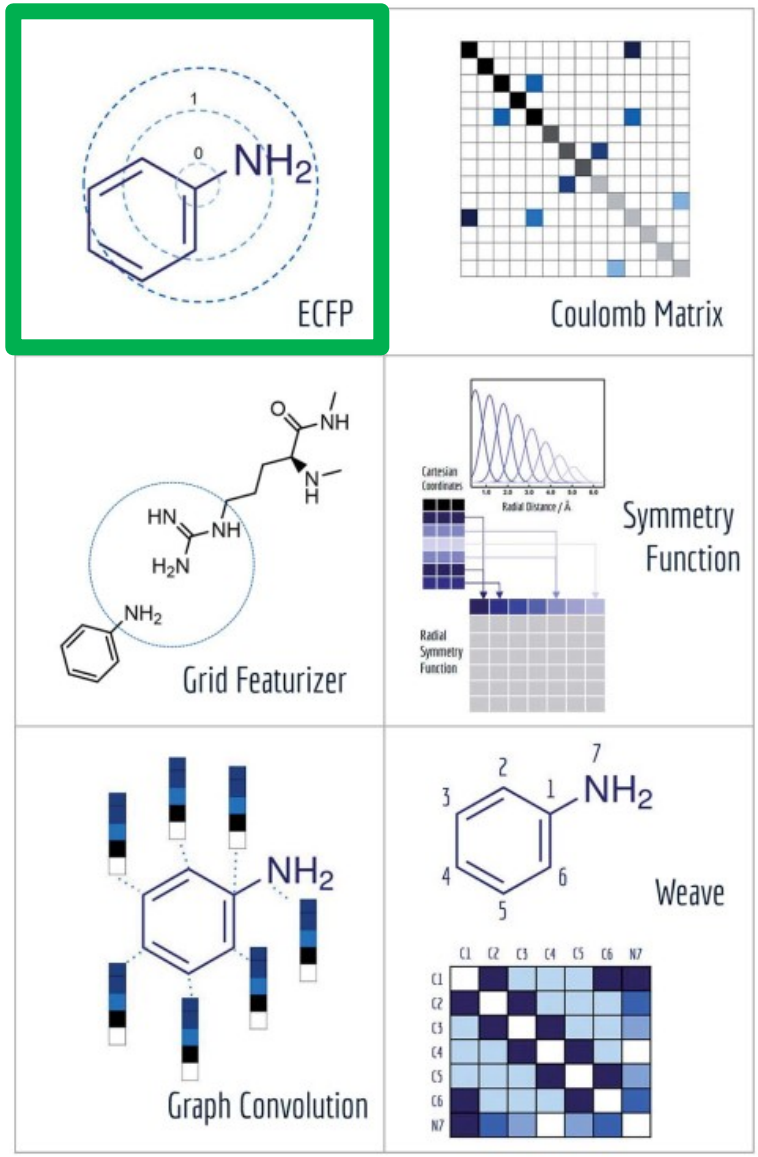
Featurization Methods in MoleculeNet



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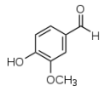
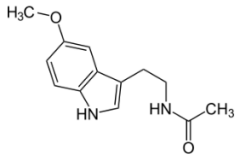
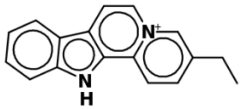
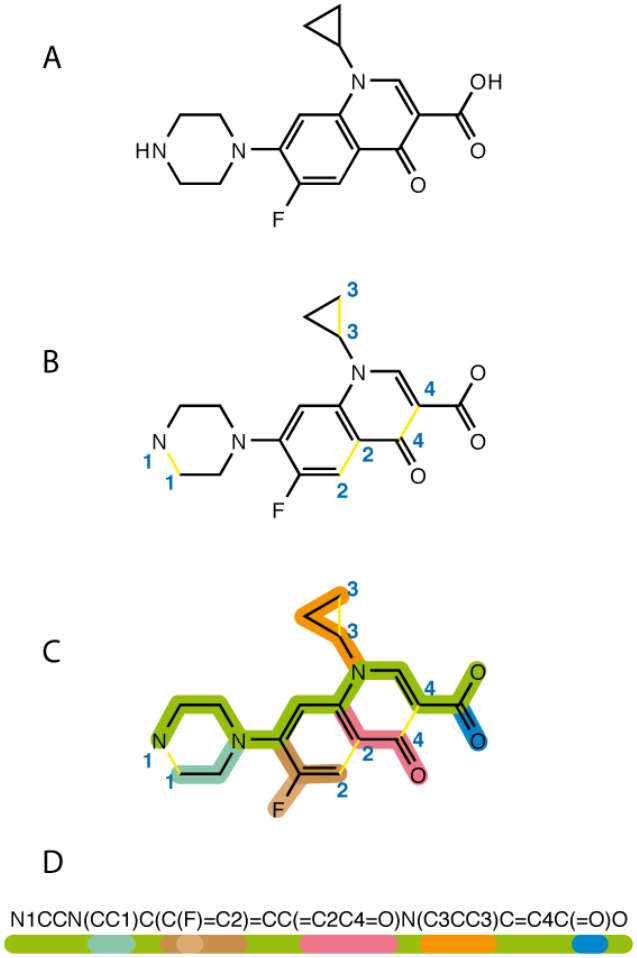
SMILES

- The simplified molecular-input line-entry system (SMILES)
- A valence model of a molecule

Structure	SMILES Formula
N≡N	`N#N`
CH_3–N=C=O	`CN=C=O`
$Cu^{2+}SO_4^{2-}$	`[Cu+2].[O-]S(=O)(=O)[O-]`
	`O=Cc1ccc(O)c(OC)c1` `COCc1cc(C=O)ccc1O`
	`CC(=O)NCCC1=CNc2c1cc(OC)cc2` `CC(=O)NCCc1c[nH]c2ccc(OC)cc12`
	`CCc(c1)ccc2[n+]1ccc3c2[nH]c4c3cccc4` `CCc1c[n+]2ccc3c4ccccc4[nH]c3c2cc1`



SMILES

- It can helpful when representing a molecule, but not sufficient for machine learning tasks.
  - Lack electronic charges or topological features.
- A core challenge in molecular machine learning is to effectively encode molecules into fixed-length vectors.
- MoleculeNet contains implementation of six featurization methods.

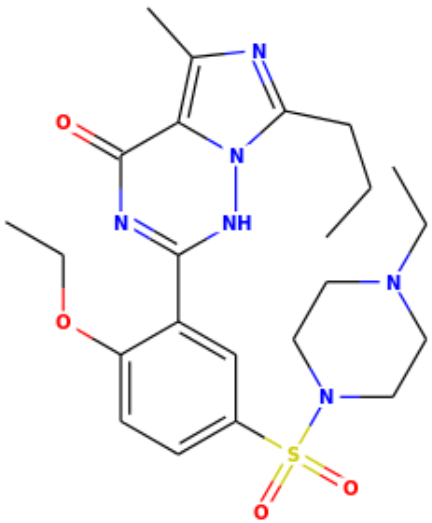
Wu, Zhenqin, Bharath Ramsundar, Evan N. Feinberg, Joseph Gomes, Caleb Geniesse, Aneesh S. Pappu, Karl Leswing, and Vijay Pande. "MoleculeNet: a benchmark for molecular machine learning." Chemical science 9, no. 2 (2018): 513-530.

1-D Feature Representations

- These representation are a collection of experimental and calculated molecular properties.
- They do not take into account the structure and bonds.
- Often, they are used for simple classification.
- In some cases, they work well.
  - E.g. the partition coefficient (ratio of solubility of two different substances)

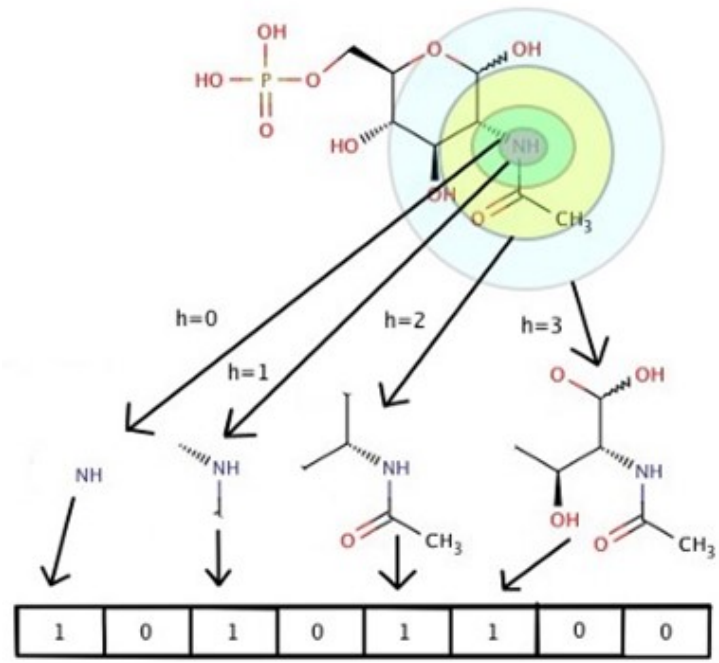
2-D Feature Descriptors

- The 2-D descriptors take into account the covalent and aromatic bonds, but not the spatial coordinates.



2D Descriptors: Fingerprints

- Fingerprinting is mapping variable-size molecular structures to a fixed-size vector (e.g. 1024 bits).
- An iterative approach
  - Diameter increasing

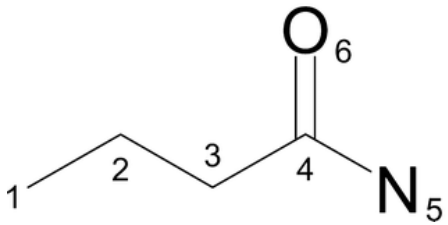


2D Descriptors: Fingerprints

- There are several fingerprinting methods, including circular fingerprint methods.
  - Each atom is examined along with its neighbors at a distance of 1, 2, ...
  - A function of atom properties (e.g., atom type) and its immediate neighborhood is computed.
  - Resulting function is hashed into a bit vector.
- A popular circular method is the extended circular fingerprints (ECFPx, x is the maximum diameter).

Fingerprints Assignment

- The initial assignment is done based on daylight atomic invariant rule:
  - the number of immediate neighbors who are “heavy” (non-hydrogen) atoms,
  - the valence minus the number of hydrogens,
  - the atomic number,
  - the atomic mass,
  - the atomic charge,
  - and the number of attached hydrogens (both implicit and explicit).
- These values are hashed into a single 32-bit integer value.

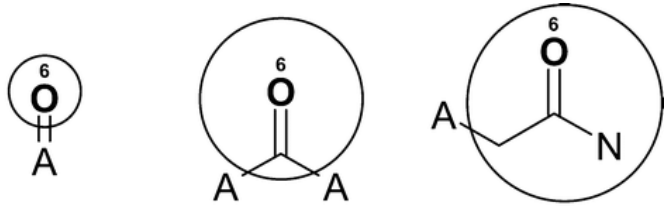


1: 734603939
2: 1559650422
3: 1559650422
4: -1100000244
5: 1572579716
6: -1074141656

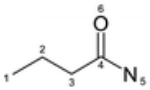
David Rogers and Mathew Hahn. Journal of Chemical Information and Modeling 2010 50 (5), 742-754

Fingerprint Iteration

- The iterative updating process generates features that represent each atom within larger and larger circular substructural neighborhoods.
- Conceptually, as the process is repeated, the feature denoted by an atom identifier represents an atom-centered substructure of increasing size.



Iteration 0 Iteration 1 Iteration 2

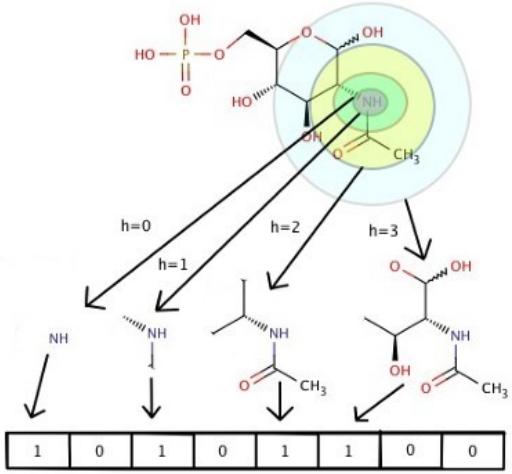


> <ECFP_0>	> <ECFP_2>	> <ECFP_4>	> <ECFP_6>
734603939	734603939	734603939	734603939
1559650422	1559650422	1559650422	1559650422
-1100000244	-1100000244	-1100000244	-1100000244
1572579716	1572579716	1572579716	1572579716
-1074141656	-1074141656	-1074141656	-1074141656
	863188371	863188371	863188371
	-1793471910	-1793471910	-1793471910
	-1789102870	-1789102870	-1789102870
	-1708545601	-1708545601	-1708545601
	-932108170	-932108170	-932108170
	2099970318	2099970318	2099970318
		-87618679	-87618679
		1112638790	1112638790
		-627599602	-627599602

David Rogers and Mathew Hahn. Journal of Chemical Information and Modeling 2010 50 (5), 742-754

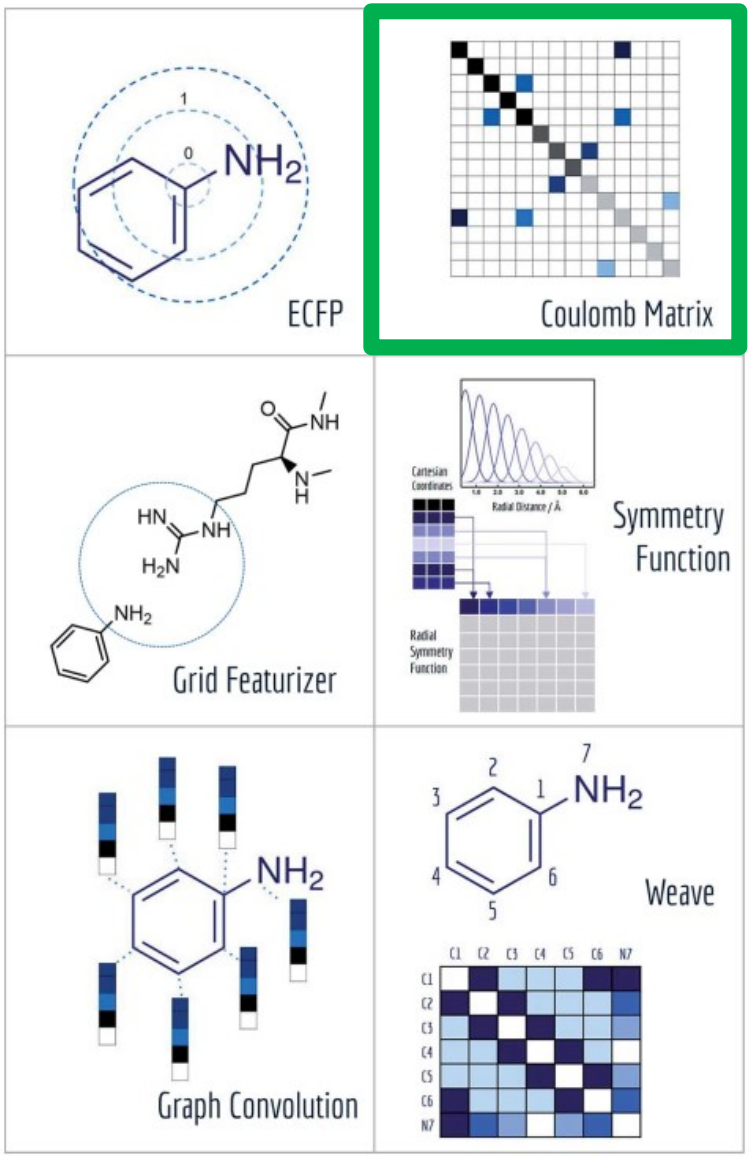
ECFP Application

- Similarity search can be easily done by comparing two bit vectors in an efficient manner.
- The representation is not unique, two completely different molecules can have the same representation.



Read more here

Featurization Methods in MoleculeNet



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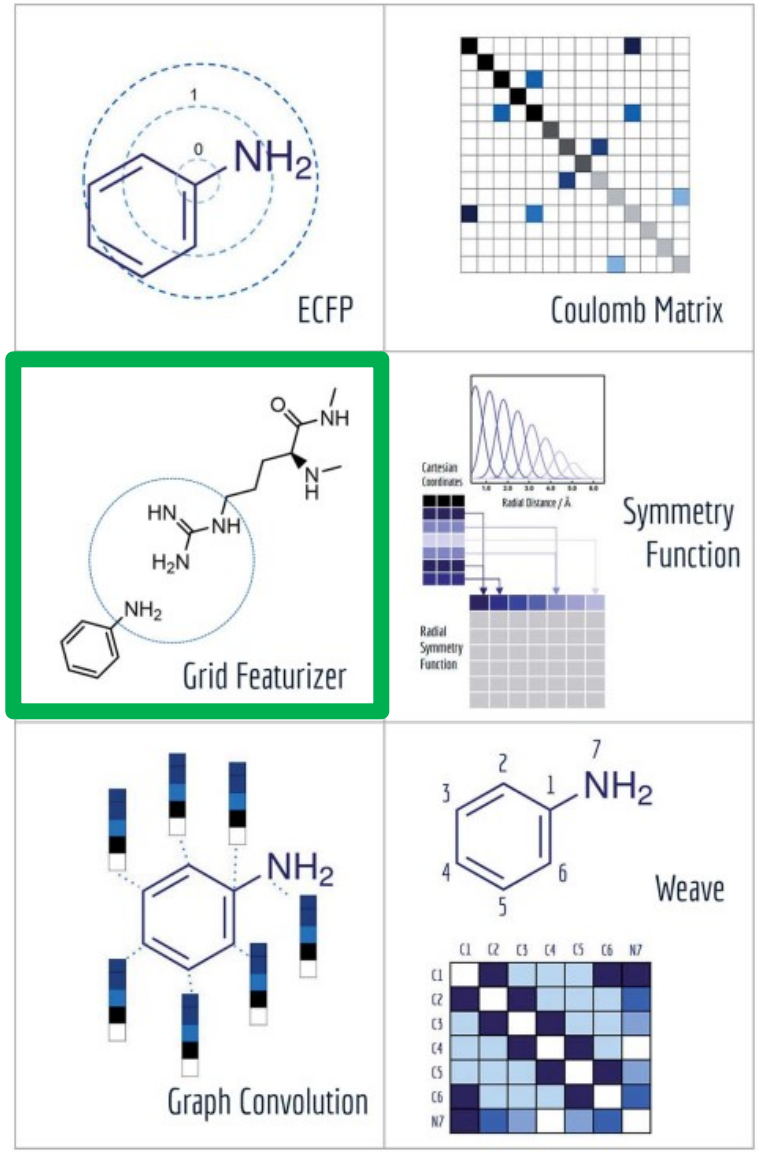
Coulomb Matrix

- Constructed using the nuclear charges and distances.
- A matrix M is constructed using the following equation.
  - Z is the nuclear charge, and R refers to Cartesian coordinates.

$$M_{IJ} = \begin{cases} 0.5 Z_I^{\,2.4} & \text{for } I = J \\ \dfrac{Z_I Z_J}{\left| \boldsymbol{R}_I - \boldsymbol{R}_J \right|} & \text{for } I \neq J \end{cases}$$

Featurization Methods in MoleculeNet



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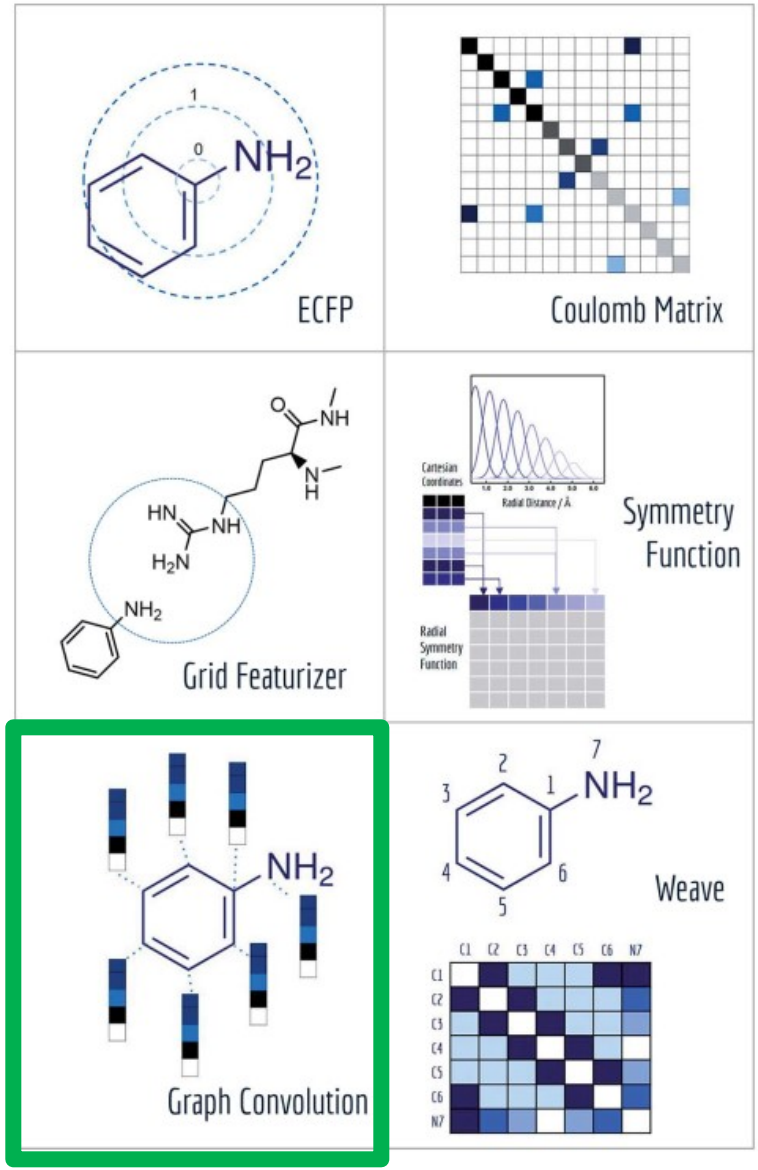
Grid Featurization

- DeepChem has a grid featurization tool based on *RdKitGridFeaturizer().*
- It searches for presence of chemical interactions and constructs a feature vector that contains the counts of such interactions.
  - Hydrogen bonds,
  - Salt bridges between amino acids,
  - Pi-stacking between aromatic rings.

Featurization Methods in MoleculeNet



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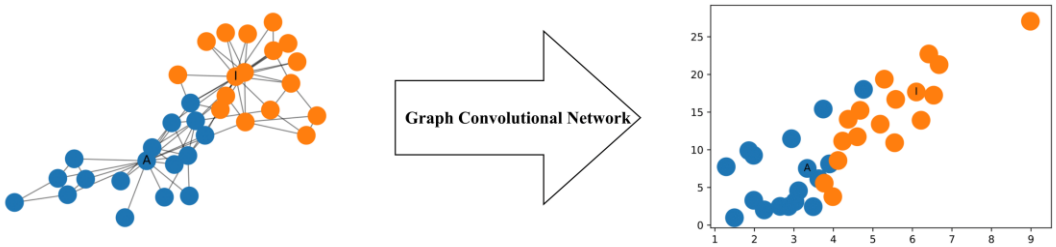
Graph Convolutional Networks

- A neural network operating on graphs with input:
  - X: a matrix of [nodes × node_features]
  - A: adjacency matrix of [nodes × nodes]



Description and Image based on this Link

X is per-atom features of each graph node

A is the atom adjacency matrix

H is the feature map for all atoms

Graph Convolutional Neural Network (GCNN)

1 bond length away

$$H^{(1)} = ReLU\left(W^{(1)} \cdot A \cdot X\right)$$

2 bond lengths away

$$H^{(2)} = ReLU\left(W^{(2)} \cdot A \cdot H^{(1)}\right)$$

$$\vdots$$

K bond lengths away

$$H^{(K)} = ReLU\left(W^{(K)} \cdot A \cdot H^{(K-1)}\right)$$

Sum over per atom features

$x^{(NN)}$ is convolutional "fingerprint" of entire molecule

$$x^{(NN)} = \sum_{atoms} H^{(K)}$$

$$h^{(1)} = ReLU\left(W^{(1)} \cdot x^{(NN)}\right)$$

$$h^{(2)} = ReLU\left(W^{(2)} \cdot h^{(1)}\right)$$

$$\vdots$$

K fully connected layers

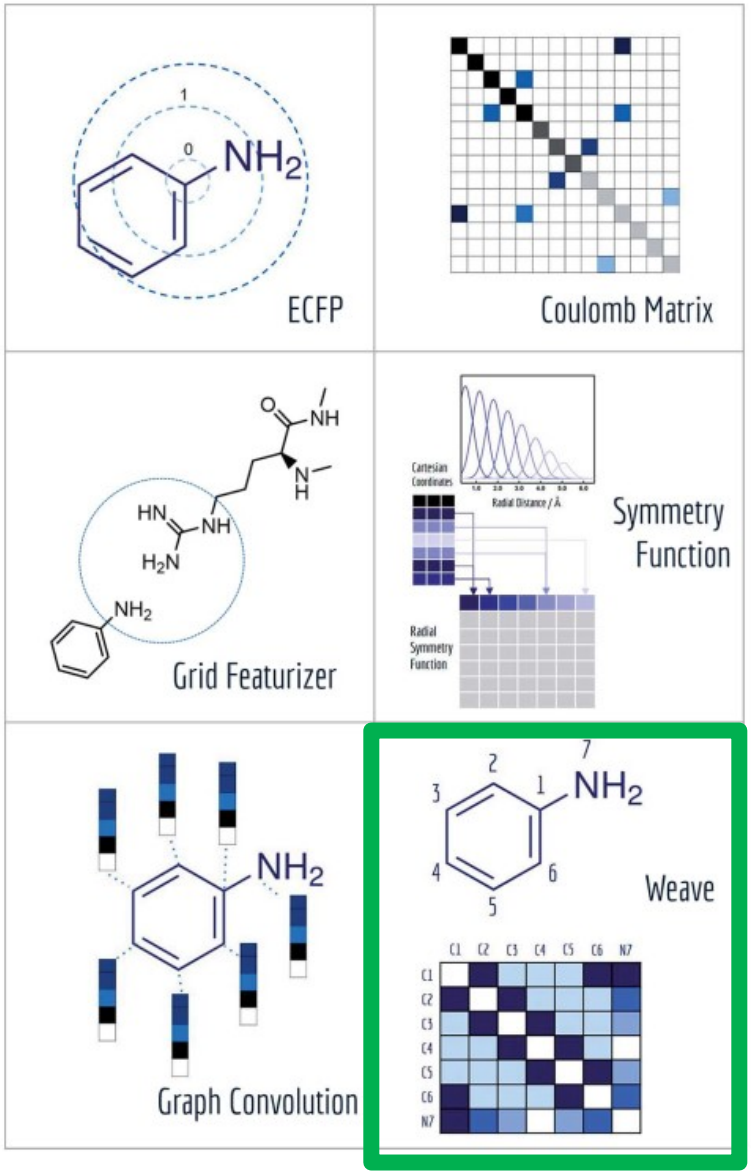
$$h^{(K)} = ReLU\left(W^{(K)} \cdot h^{(K-1)}\right)$$

Credit: https://mit6874.github.io/assets/slides/6.874-lecture-14-2019.pdf

Graph Convolutions

- Convolutions in graphs are more challenging, we are dealing with abstract concepts, with no notion of sliding up or down the image!
- Two types of graph convolutions
  - Spatial
  - Spectral

Featurization Methods in MoleculeNet



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Weave

- Similar to graph convolutions, the weave featurization encodes both local chemical environment and connectivity of atoms in a molecule.
- Difference:
  - Atomic feature vectors are exactly the same.
  - More detailed pair features instead of neighbor listing.
  - The weave featurization calculates a feature vector for each pair of atoms in the molecule, including bond properties (if directly connected), graph distance and ring info, forming a feature matrix.

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Applications

Predicting Protein Structures

- Homology modeling
  - If two proteins are homolog (near relatives), they probably have similar structures.
  - This works well for the overall shape, but often gets the details wrong.
- Physical Modeling
  - Using knowledge of physics laws to predict possible conformation
  - Computationally expensive
  - Will often predict the right structure, but not always.

Protein Binding

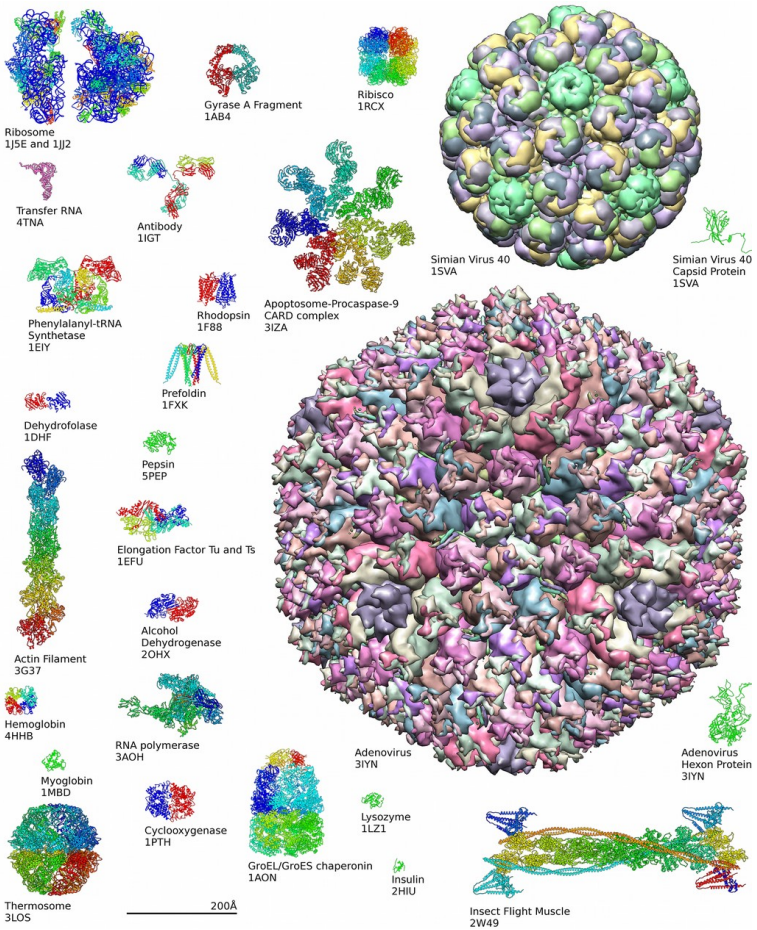
- Protein binding is very important.
  - E.g. Signaling transduction
- It involves lots of very specific details.
  - E.g. changing a few atoms can determine if a molecule binds to a protein or not.

Biophysical Featurization

1. Grid Featurization
   - It explicitly searches a 3D structure for the presence of critical physical interactions such as hydrogen bonds or salt bridges.
   - We can rely on a wealth of known facts.
   - Yet, bound by known physics.
2. Atomic Featurization
   - It provides a processed representation of the 3D positions and identities of all atoms.
   - It must learn to identify critical physical interactions,
   - Yet, feasible to detect new patterns of interesting behavior

Protein Data Bank (PDB)

- The primary repository for known protein structures
- It contains over 142,000 structures.
  - Far less than what we want.



PDBind Dataset

- The PDBind dataset contains a large number of biomolecular crystal structures.
- About 15,000 complex structures, each annotated with the binding affinity measure.
- We will look at the problem of predicting the binding affinity in protein-ligand complexes.
- Design of better machine learning models to accurately predict the thermodynamic behavior of these systems is still an open problem.

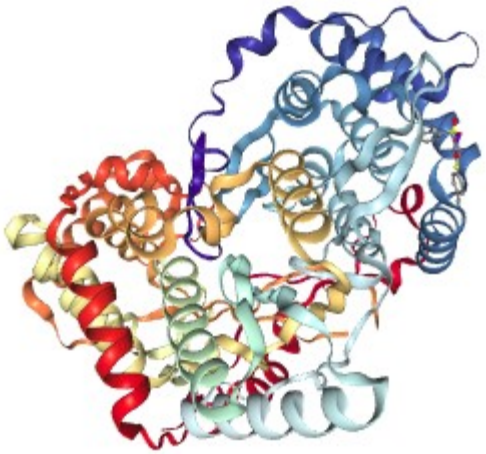
PDB Files

- Protein structures are stored in PDB files.
  - Text files containing description of the atoms in the structure and their positions.
  - Often malformed, as experiments fail to have adequate resolution to completely specify a portion of the protein.
  - PDB files can be difficult to understand, so we use visualization packages.
    - NGLview

NGLview

```
SEQRES  27 B  570  PHE THR GLU ALA MET THR ARG TYR SER ALA PRO PRO GLY
SEQRES  28 B  570  ASP PRO PRO GLN PRO GLU TYR ASP LEU GLU LEU ILE THR
SEQRES  29 B  570  SER CYS SER SER ASN VAL SER VAL ALA HIS ASP ALA SER
SEQRES  30 B  570  GLY LYS ARG VAL TYR TYR LEU THR ARG ASP PRO THR THR
SEQRES  31 B  570  PRO LEU ALA ARG ALA ALA TRP GLU THR ALA ARG HIS THR
SEQRES  32 B  570  PRO VAL ASN SER TRP LEU GLY ASN ILE ILE MET TYR ALA
SEQRES  33 B  570  PRO THR LEU TRP ALA ARG MET ILE LEU MET THR HIS PHE
SEQRES  34 B  570  PHE SER ILE LEU LEU ALA GLN GLU GLN LEU GLU LYS ALA
SEQRES  35 B  570  LEU ASP CYS GLN ILE TYR GLY ALA CYS TYR SER ILE GLU
SEQRES  36 B  570  PRO LEU ASP LEU PRO GLN ILE ILE GLU ARG LEU HIS GLY
SEQRES  37 B  570  LEU SER ALA PHE SER LEU HIS SER TYR SER PRO GLY GLU
SEQRES  38 B  570  ILE ASN ARG VAL ALA SER CYS LEU ARG LYS LEU GLY VAL
SEQRES  39 B  570  PRO PRO LEU ARG VAL TRP ARG HIS ARG ALA ARG SER VAL
SEQRES  40 B  570  ARG ALA ARG LEU LEU SER GLN GLY GLY ARG ALA ALA THR
SEQRES  41 B  570  CYS GLY LYS TYR LEU PHE ASN TRP ALA VAL LYS THR LYS
SEQRES  42 B  570  LEU LYS LEU THR PRO ILE PRO ALA ALA SER GLN LEU ASP
SEQRES  43 B  570  LEU SER GLY TRP PHE VAL ALA GLY TYR SER GLY GLY ASP
SEQRES  44 B  570  ILE TYR HIS SER LEU SER ARG ALA ARG PRO ARG
HET    CCT  A1001      27
HET    CCT  B2001      27
HETNAM     CCT 5-(4-CYANOPHENYL)-3-{[(2-METHYLPHENYL)
HETNAM   2 CCT  SULFONYL]AMINO}THIOPHENE-2-CARBOXYLIC ACID
FORMUL   3  CCT    2(C19 H14 N2 O4 S2)
FORMUL   5  HOH   *754(H2 O)
HELIX    1   1 LEU A   26  LEU A   31  1                                   6
HELIX    2   2 HIS A   33  ASN A   35  5                                   3
HELIX    3   3 THR A   41  ARG A   43  5                                   3
HELIX    4   4 SER A   44  THR A   53  1                                  10
HELIX    5   5 ASP A   61  SER A   76  1                                  16
HELIX    6   6 SER A   84  LEU A   91  1                                   8
HELIX    7   7 GLY A  104  ASN A  110  1                                   7
HELIX    8   8 SER A  112  ASP A  129  1                                  18
HELIX    9   9 ASP A  164  GLY A  188  1                                  25
HELIX   10  10 SER A  189  TYR A  195  5                                   7
HELIX   11  11 SER A  196  SER A  210  1                                  15
```

PDB File



Other Visualization Tools

- Note that there are other tools used in professional drug discovery.
  - VMD, PyMOL, Chimera
- NGLview is nicely integrated into Jupyter and is open source.