Frederick National Laboratory
for Cancer Research

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Predicting Drug Function Using Small-Molecule Structure Information

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BIDS, FNLCR

(announcement coming soon)

DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

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Acknowledgements

- NCI-DOE Pilot-1 Team

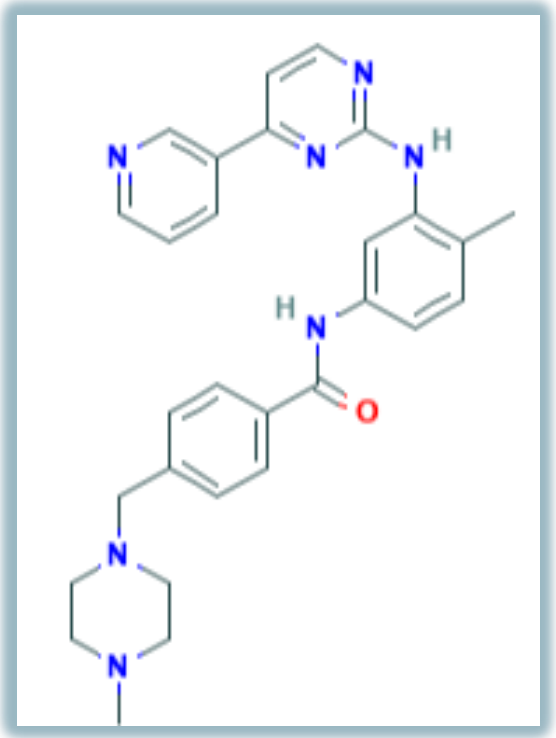
- BIDS
  - Drs. George Zaki, Andrew Weissman and Eric Stahlberg
  - Colleagues who reviewed the material

Introduction

- This is part of the NCI-DOE knowledge/capability transfer efforts
- Share tools/techniques/solutions for cancer related problems. We often take a test-case and show how it works
- You will be able to take the test-case (code/scripts) and tune it to your needs

Objectives

- Knowledge-transfer of reproducible Machine-Learning frameworks for modeling drug-discovery problems
  - User-friendly, run across multiple-OS etc.
  - A Notebook that supports multiple languages
- Identify drugs that belong to a Pharmacological Class using chemical properties (*in-silico*)
- Example
  - Given a drug (ex. Imatinib) in the form of chemical structure, can we predict, its drug function?

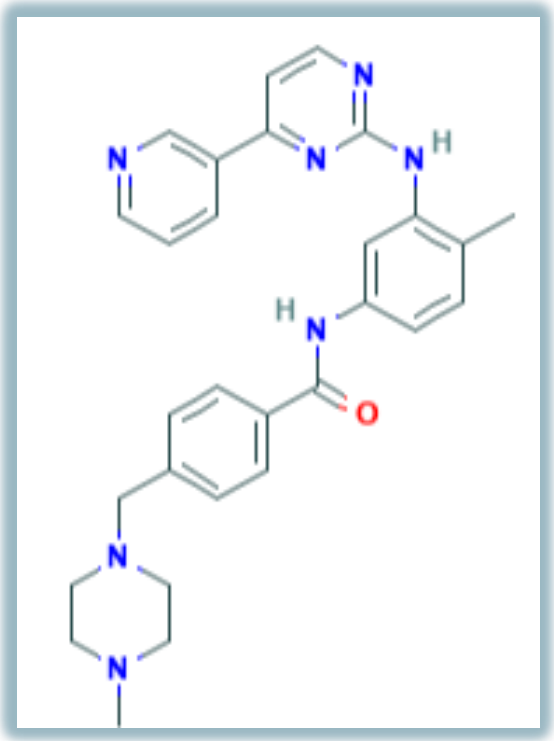


Antineoplastic Agents: Substances that inhibit or prevent the proliferation of NEOPLASMS.

CC1=C(C=C(C=C1)NC(=O)C2=CC=C(C=C2)CN3CCN(CC3)C)NC4=NC=CC(=N4)C5=CN=CC=C5.CS(=O)(=O)O

Objectives → ?s

- Where do we begin and ?s
  - Drug molecules: List of compounds
  - A definition of “How to define drug function?”
  - A list of properties associated with molecules



Antineoplastic Agents: Substances that inhibit or prevent the proliferation of NEOPLASMS.

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Why are we interested in this problem?

- Closely related to another area in Drug-Discovery called Drug repurposing

> "*Drug repurposing is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication*" *Nat. Rev. 18, 41, 2019*

Drug-repurposing/Repositioning/Reprofiling/Re-tasking

"*Drug repurposing is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication*"
Nat. Rev. 18, 41, 2019

Drug-repurposing/Repositioning/Reprofiling/Re-tasking

Zhou et al. *Cell Discovery* (2020)6:14
https://doi.org/10.1038/s41421-020-0153-3

Cell Discovery
www.nature.com/celldisc

ARTICLE Open Access

Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2

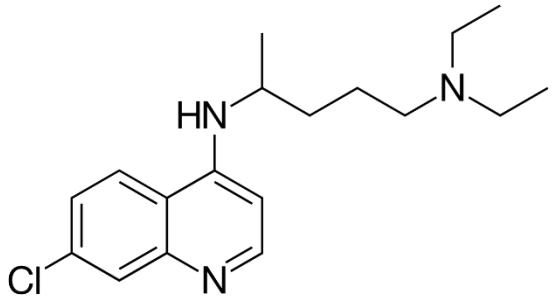
Yadi Zhou[1], Yuan Hou[1], Jiayu Shen[1], Yin Huang[1], William Martin[1] and Feixiong Cheng[1,2,3]

Drug repurposing: progress, challenges and recommendations

*Sudeep Pushpakom[1], Francesco Iorio[2], Patrick A. Eyers[3], K. Jane Escott[4], Shirley Hopper[5], Andrew Wells[6], Andrew Doig[7], Tim Guilliams[8], Joanna Latimer[9], Christine McNamee[1], Alan Norris[1], Philippe Sanseau[10], David Cavalla[11] and Munir Pirmohamed[1]**

NATURE REVIEWS | DRUG DISCOVERY VOLUME 18 | JANUARY 2019 | 41

Chloroquine, a malarial drug, against Coronavirus?



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The New York Times

MATTER

Scientists Identify 69 Drugs to Test Against the Coronavirus

Two dozen of the medicines are already under investigation. Also on the list: chloroquine, a drug used to treat malaria.

Drug-repurposing/Repositioning/Reprofiling/Re-tasking

NATURE REVIEWS | DRUG DISCOVERY VOLUME 18 | JANUARY 2019 | 41

Drug Name	Original Indication	New Indication	Date of Approval	Repurposing approach used	Comments
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	First anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair-loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sale for minoxidil were US $860 million in 2016

Test case example

Learning Drug Functions from Chemical Structures with Convolutional Neural Networks and Random Forests

Jesse G. Meyer*, Shengchao Liu, Ian J. Miller, Joshua J. Coon and Anthony Gitter

Cite this: *J. Chem. Inf. Model.* 2019, 59, 10, 4438-4449
Publication Date: September 13, 2019
https://doi.org/10.1021/acs.jcim.9b00236
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Goals/Questions

- To identify drugs that belong to a Pharmacological Class using chemical properties (in-silico)

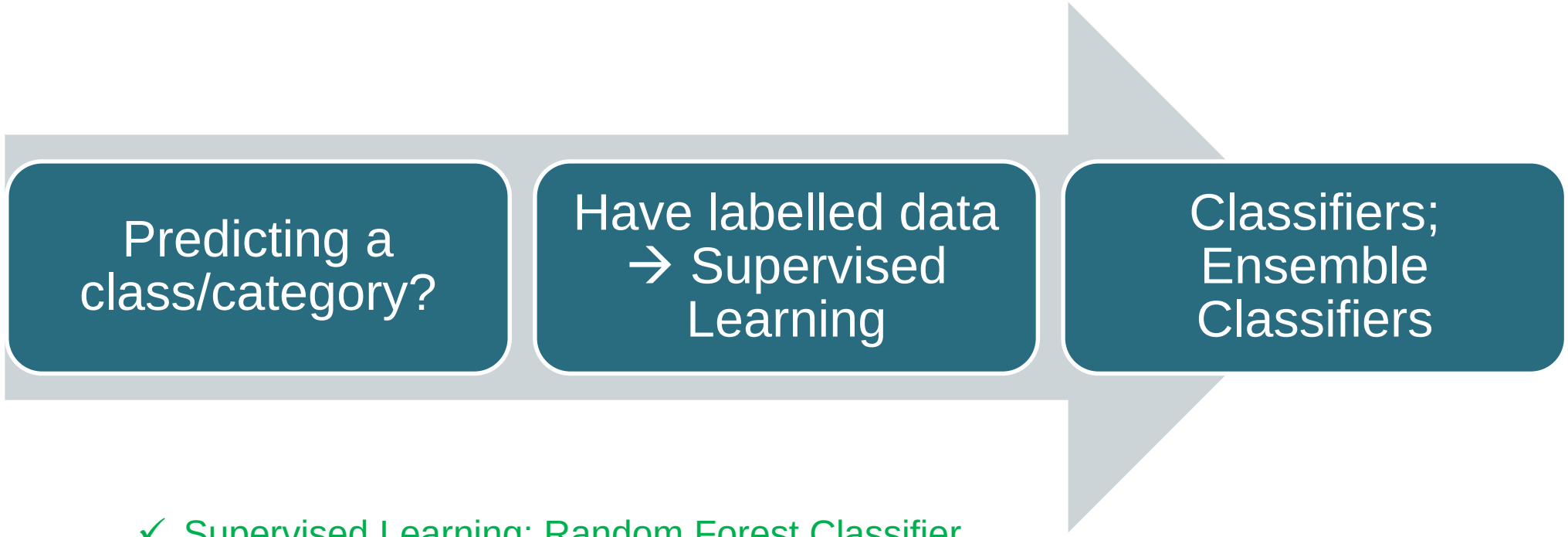
1. We want to predict outcome (Class), what estimator will be appropriate?

2. Where do we get drug-class (outcome) and the chemical structure of compounds?

3. How can we calculate Feature/property for drug molecules?

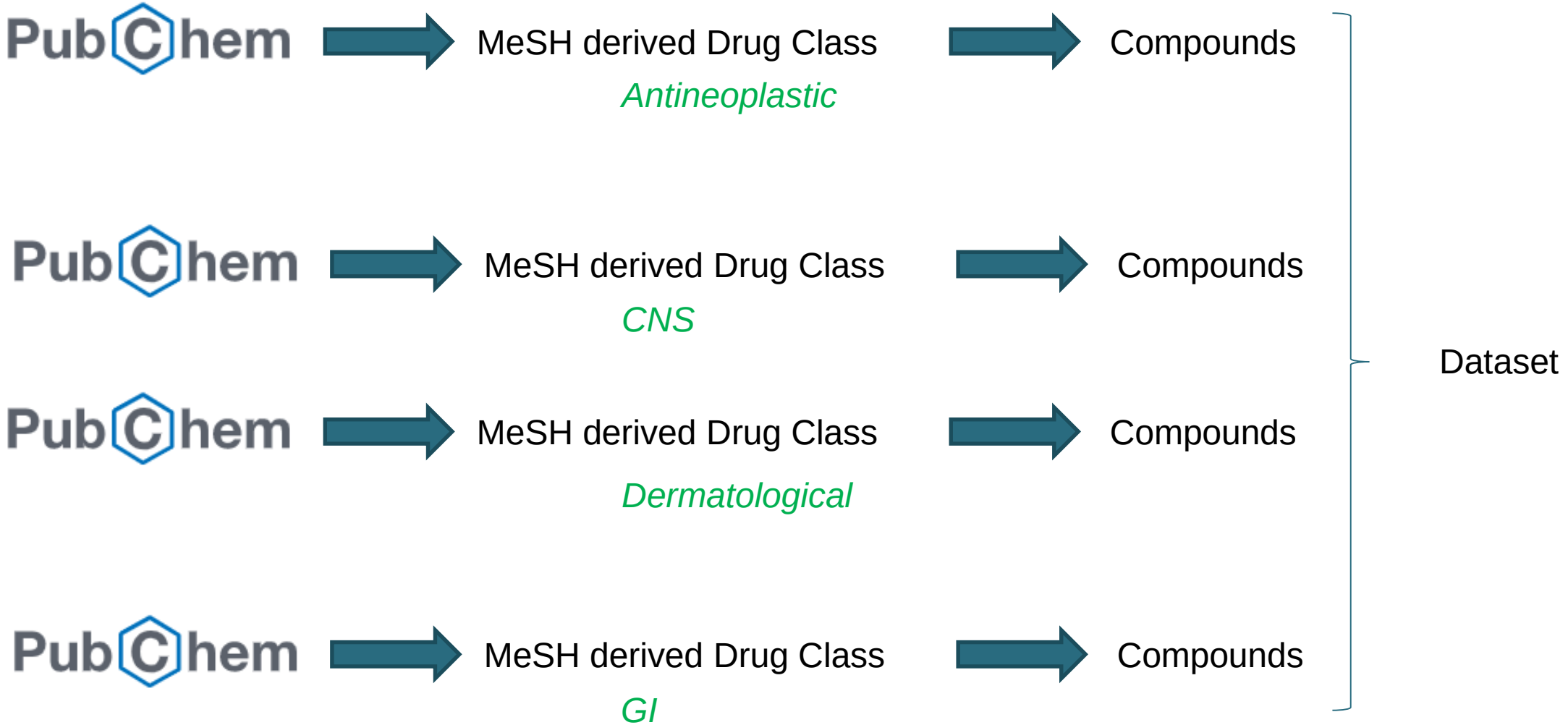
4. We will provide some tools (software libraries) that can accomplish the above tasks

1. We want to predict outcome (Class), what estimator will be appropriate?



✓ Supervised Learning; Random Forest Classifier

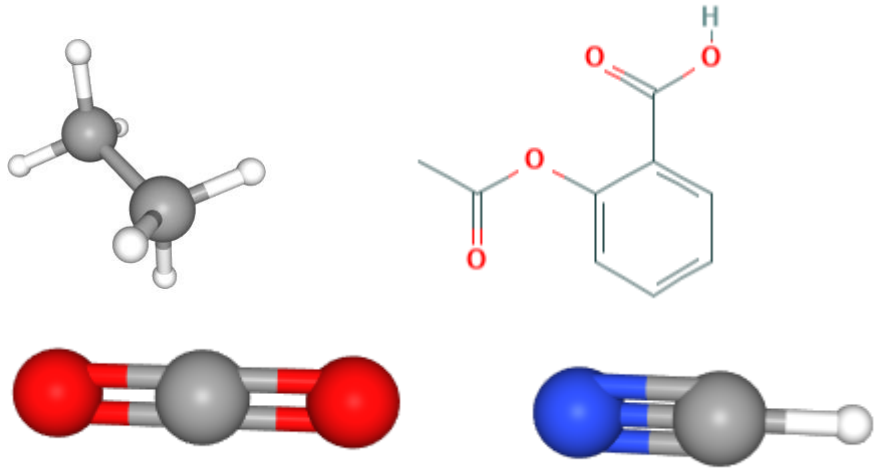
2. Where do we get drug-class (outcome) and the chemical structure of compounds?



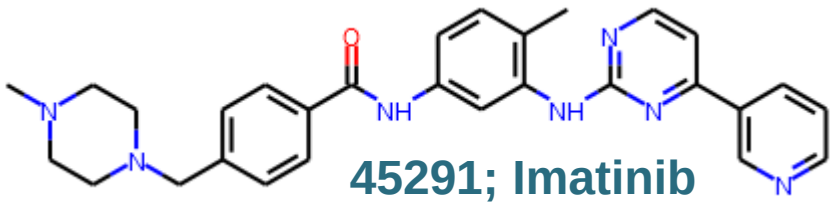
2. Where do we get drug-class (outcome) and the chemical structure of compounds?

- We need structure to compute chemical properties.
- SMILES (Simplified Molecular Input Line Entry System)
- *“ SMILES is a line notation* (a typographical method using printable characters) for entering and representing molecules and reactions.”

SMILES	Names
CC	Ethane
O=C=O	Carbon dioxide
C#N	Hydrogen Cyanide
CC(=O)OC1=CC=CC=C1C(=O)O	Aspirin

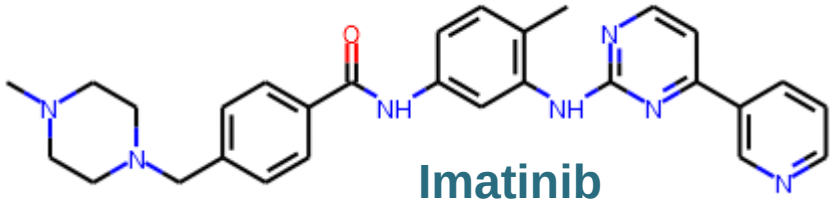


CC1=C(C=C(C=C1)NC(=O)C2=CC=C(C=C2)CN3CCN(CC3)C)NC4=NC=CC(=N4)C5=CN=CC=C5.CS(=O)(=O)O



45291; Imatinib

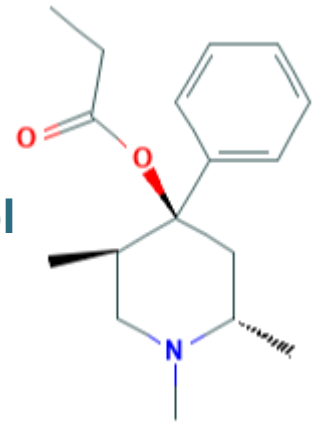
2. Where do we get drug-class (outcome) and the chemical structure of compounds?

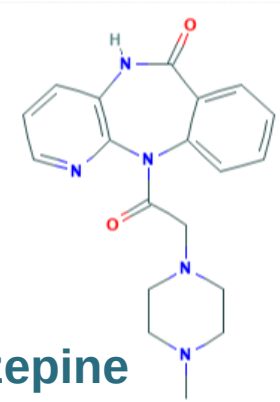


Imatinib

CID	Name	SMILES	Class
45291	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	Antineoplastic
20055107	gamma-Promedol	CCC(=O)OC1(CC(N(CC1C)C)C)C2=CC=CC=C2	CNS
5362119	lisinopril	C1=CC(=CC(=C1)C(=O)NCCO)C2=CC(=NC=N2)NC3=CC=C(C=C3)OC(F)(F)F	Cardio
4848	Pirenzepine	CN1CCN(CC1)CC(=O)N2C3=CC=CC=C3C(=O)NC4=C2N=CC=C4	GI

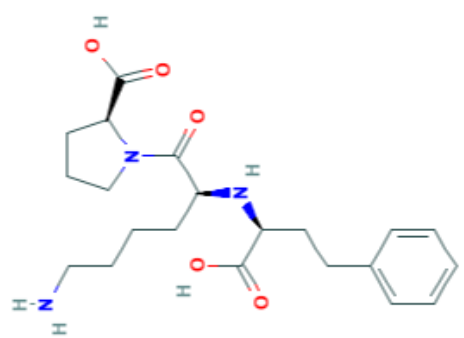
Gamma-Promedol



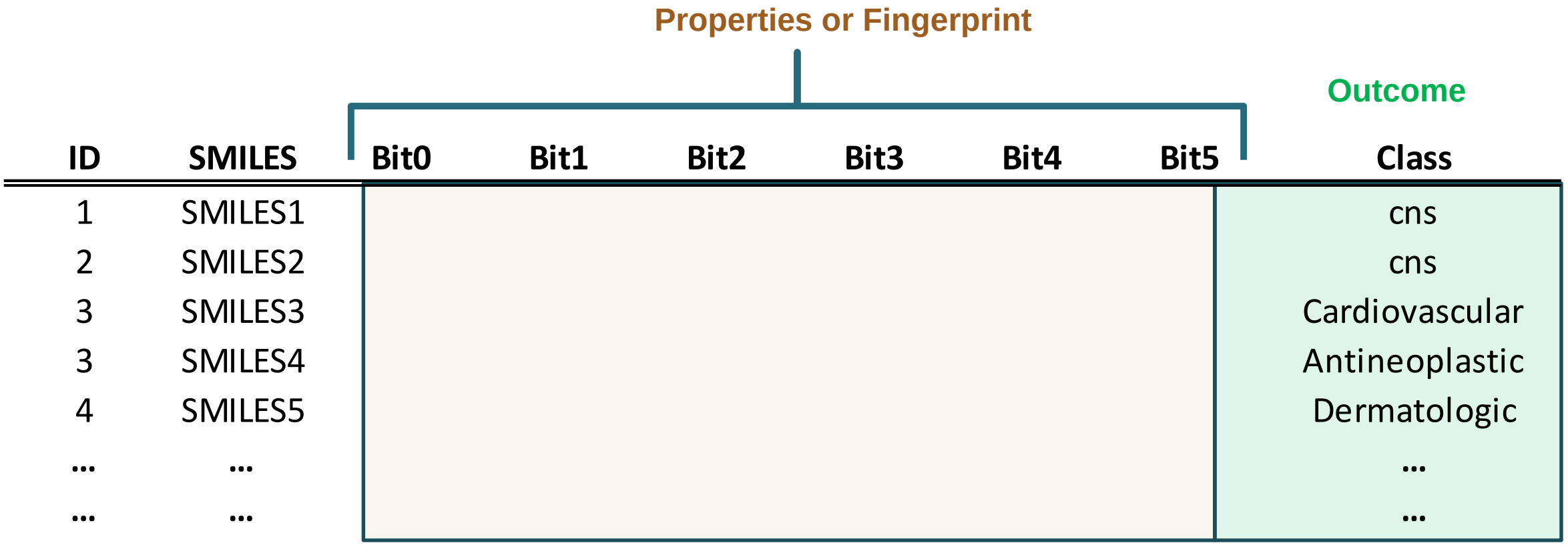


Pirenzepine

Lisinopril



3. How can we calculate Feature/property for drug molecules?



ID	SMILES	Bit0	Bit1	Bit2	Bit3	Bit4	Bit5	Class
1	SMILES1							cns
2	SMILES2							cns
3	SMILES3							Cardiovascular
3	SMILES4							Antineoplastic
4	SMILES5							Dermatologic
…	…							…
…	…							…

- ✓ Supervised Learning; Random Forest Classifier
- ✓ PubChem to gather data
- ○ Fingerprints for descriptors

3. How can we calculate Feature/property for drug molecules?

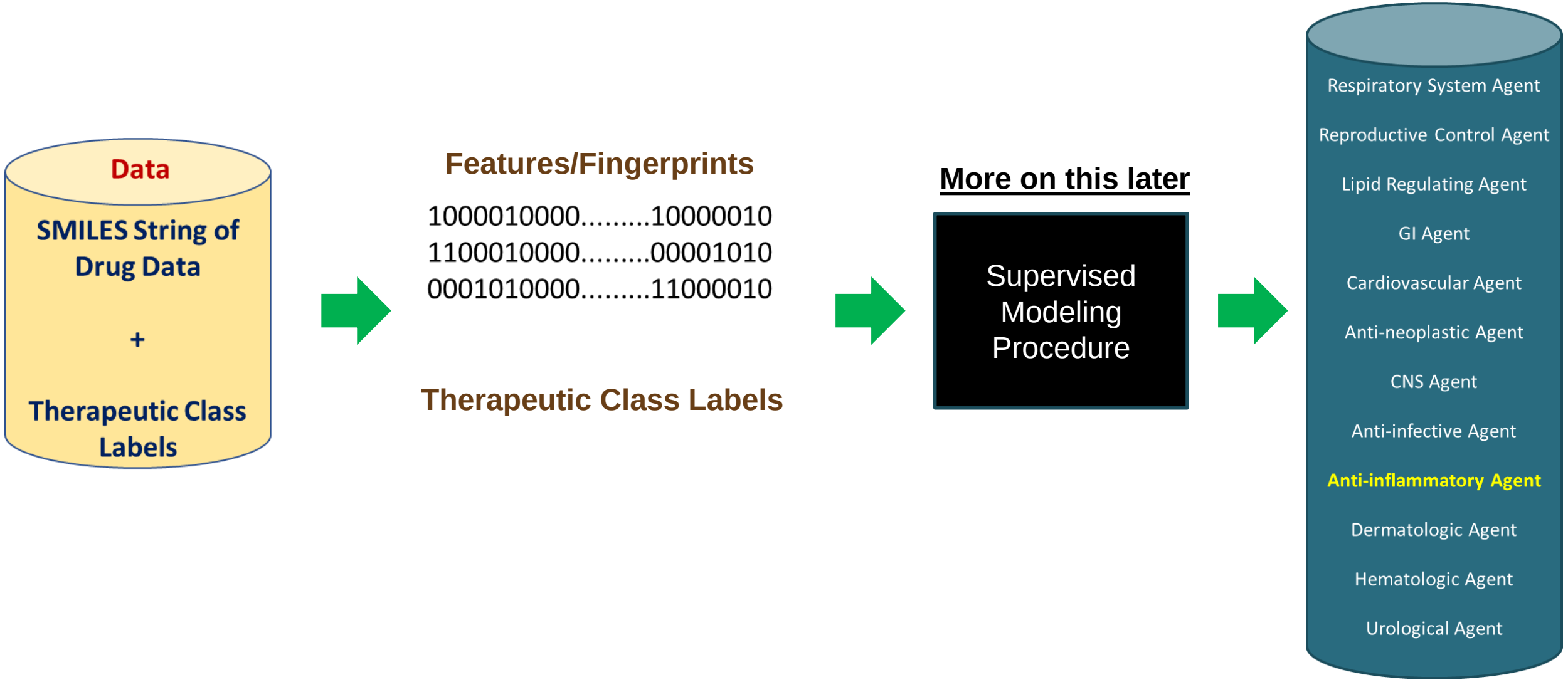
Properties or Fingerprint

Outcome

ID	SMILES	Bit0	Bit1	Bit2	Bit3	Bit4	Bit5	Class
1	SMILES1	1	1	0	1	0	1	cns
2	SMILES2	0	0	0	1	1	0	cns
3	SMILES3	1	0	0	1	0	0	Cardiovascular
3	SMILES4	1	0	0	1	1	0	Antineoplastic
4	SMILES5	1	1	0	1	1	1	Dermatologic
…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…

- ✓ Supervised Learning; Random Forest Classifier
- ✓ PubChem to gather data
- ✓ Fingerprints for descriptors

Recent efforts have showed that Molecular Fingerprints can Serve an Effective Feature Set for Machine-Learning



The property we will compute is called Molecular Fingerprint

> J Chem Inf Model, 50 (5), 742-54 2010 May 24

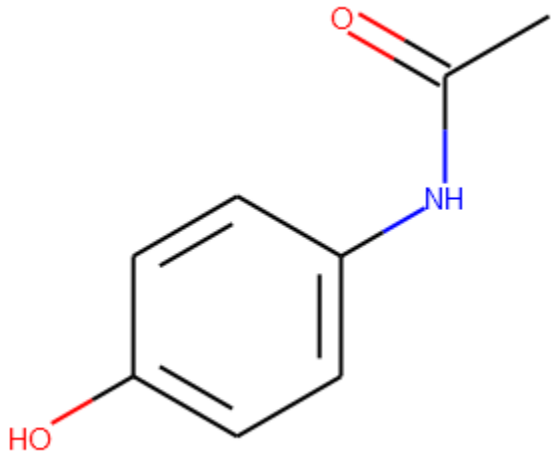
Extended-connectivity Fingerprints

David Rogers [1], Mathew Hahn

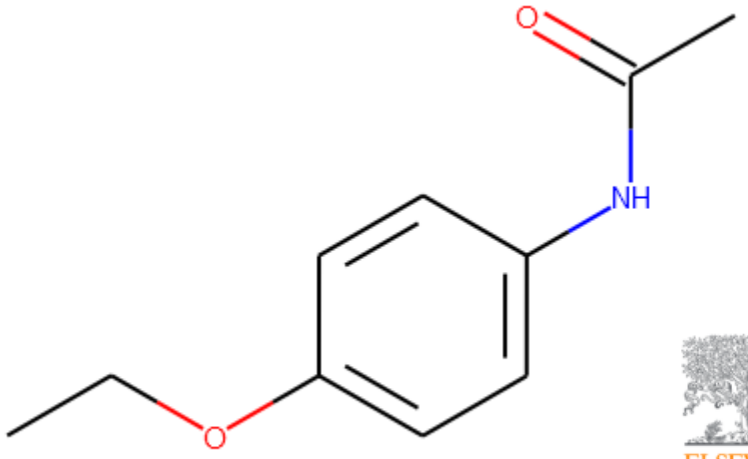
Affiliations + expand

PMID: 20426451 DOI: 10.1021/ci100050t

Molecular Fingerprints



Paracetamol



Phenacetin

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ELSEVIER

Toxicology and Applied Pharmacology
Volume 1, Issue 3, May 1959, Pages 240-249

The acute oral toxicity of phenacetin

Eldon M. Boyd [1]

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https://doi.org/10.1016/0041-008X(59)90108-5

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Morgan 2048-bit FingerPrint for Paracetamol

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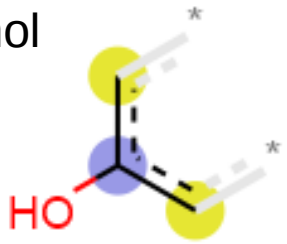
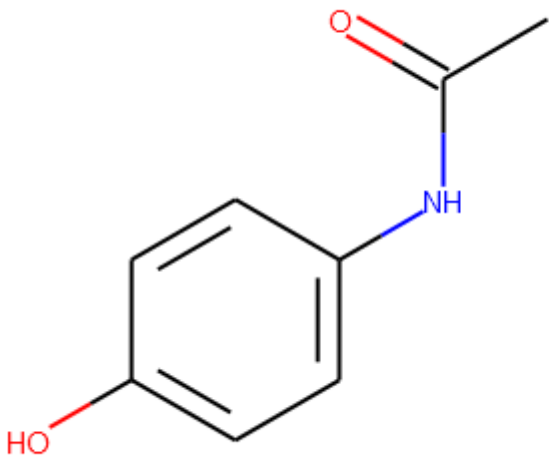
Morgan 2048-bit FingerPrint

Turned-on bits for Paracetamol [191, 245, 530, 650, 745, 807, 843, 849, 1017, 1057, 1077, 1152, 1313, 1380, 1602, 1750, 1778, 1816, 1873, 1917]

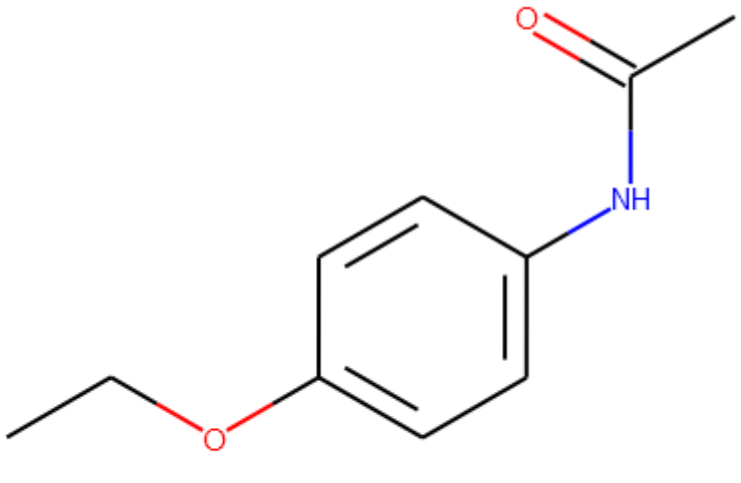
Paracetamol unique



745

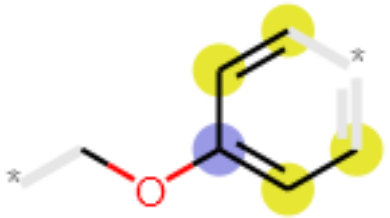


Paracetamol



Phenacetin

Phenacetin unique

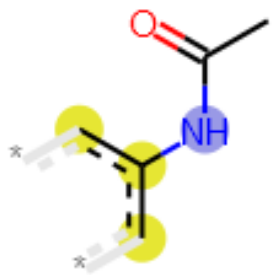


102

blue: the central atom in the environment

yellow: aromatic atoms

gray: aliphatic ring atoms



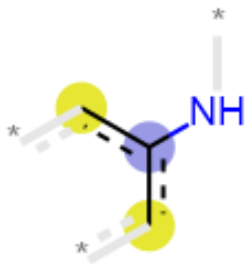
530

Underline marks common bits

Turned-bits for Pheacetin [69, 80, 102, **191**, 237, **245**, 294, 322, **530**, **650**, 695, 718, **807**, **843**, **849**, **1017**, **1057**, **1077**, **1152,** 1238, **1380**, 1452, **1750**, **1816**, **1873**, **1917**]

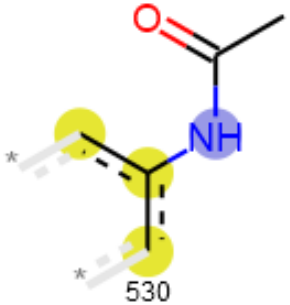
Paracetamol fingerprint collection

Turned-on bits for Paracetamol [191, 245, 530, 650, 745, 807, 843, 849, 1017, 1057, 1077, 1152, 1313, 1380, 1602, 1750, 1778, 1816, 1873, 1917]



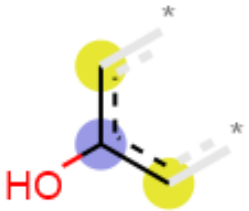
191

245



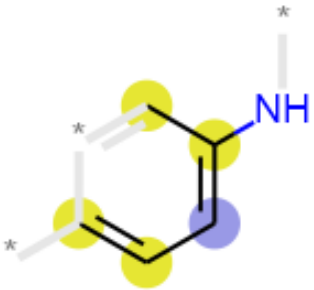
530

650

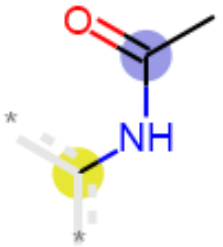


745

807



843



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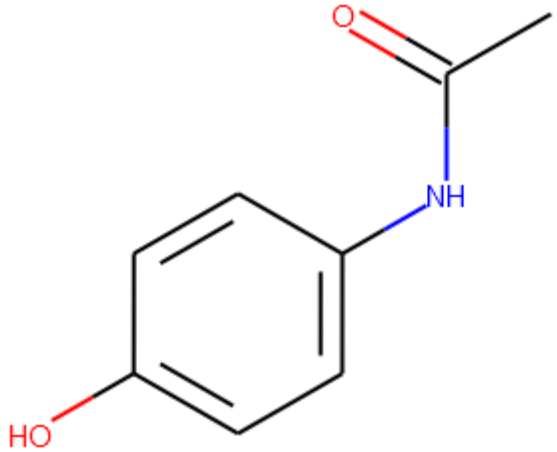
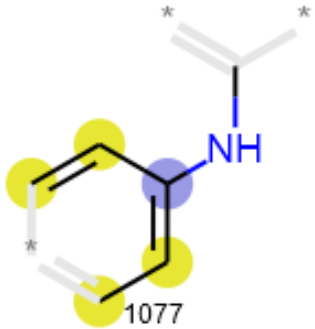


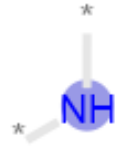
Paracetamol

1017

1057



1077



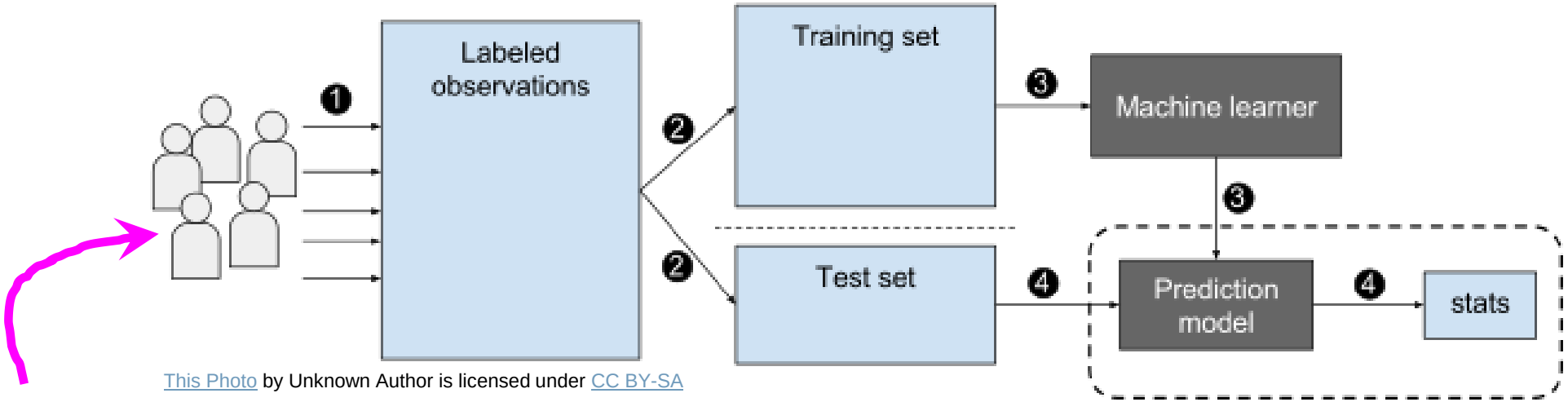
1152

Tools Review

https://github.com/ravichas/ML-predict-drugclass

Machine Learning using Supervised Learning as an example

- Randomly split the data into Training (ex. 60%) and Test set (ex. 40%)
- Using the training dataset we would like to:
  - Accurately(??) predict new or unseen case labels
  - Try to understand which inputs affect (& how) the outcome (i.e. Cancer or not)
  - Evaluate (using test set) the correctness of our predictions and inferences



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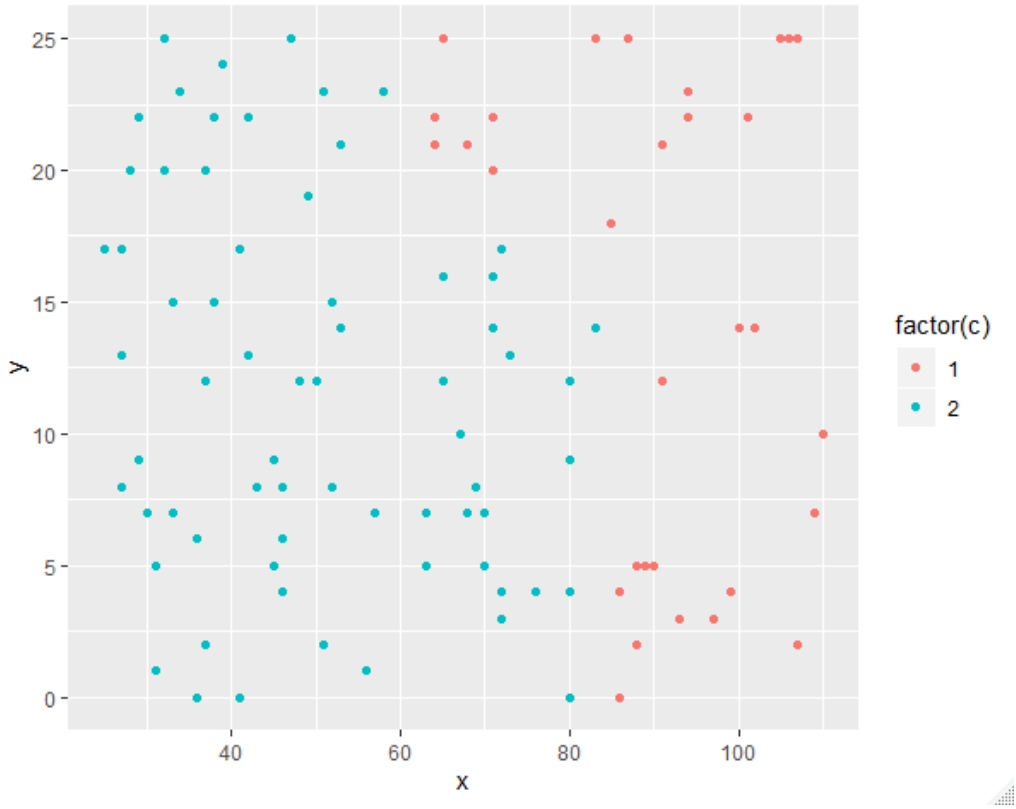
ID Bit1 Bit2 Bit3 ….. Bit2048 OUTCOME

Machine-learner: Classification

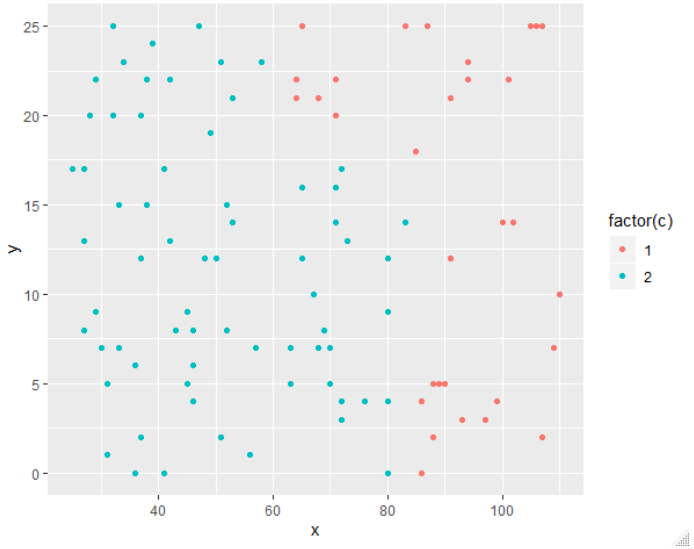
- Qualitative variables: unordered set, C,
  - Eye-color ∈ { **black, brown, blue** }
  - Given a feature vector X (fingerprint) and a qualitative outcome Y (taking values from the set in C, the task is to identify a function C(X) that predicts a value for Y
    - C(X) ∈ C
    - Takes in X and outputs one of the elements of C
  - One can also compute the probabilities of what X belongs to C

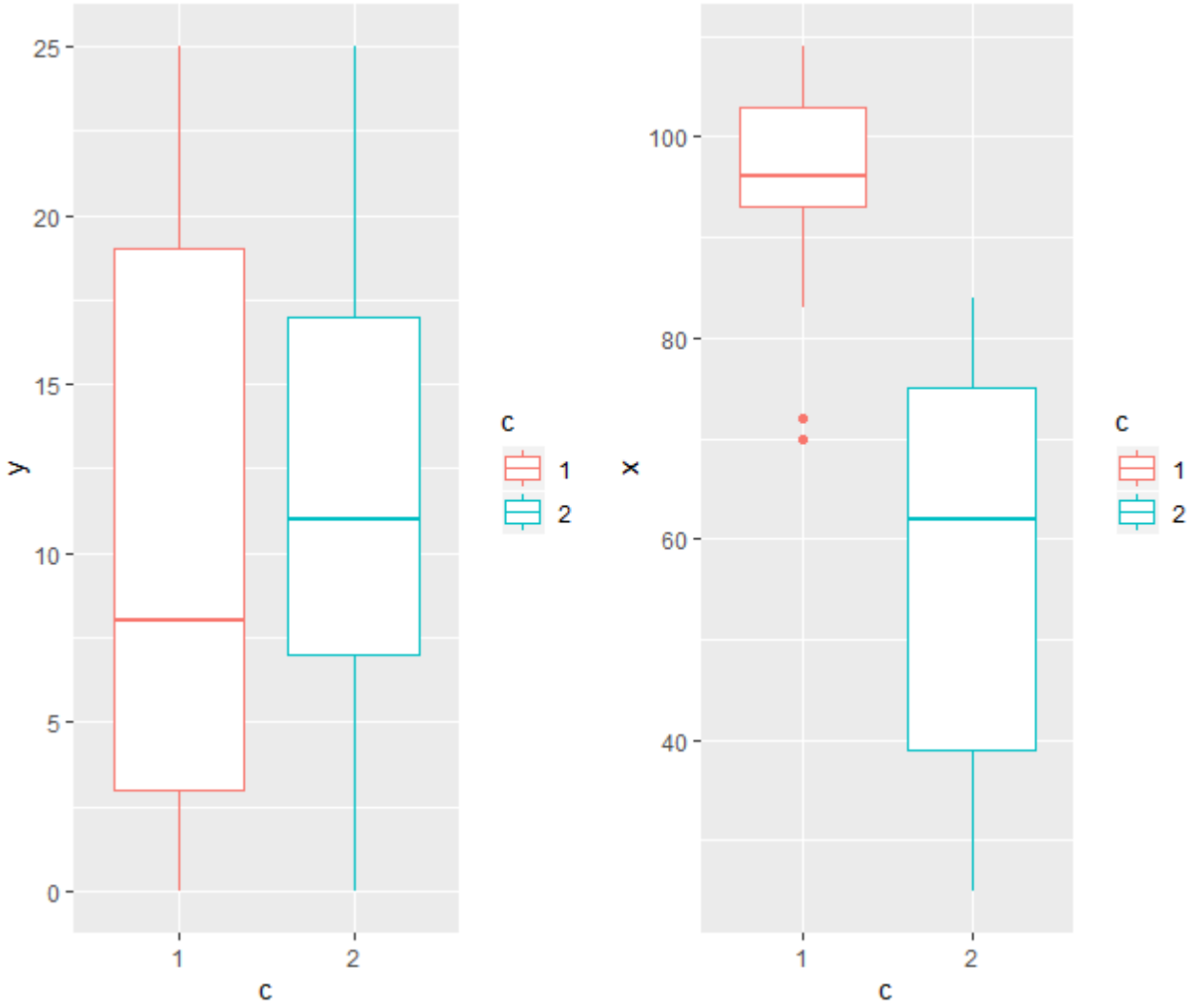
CART: Classification motivation

ID	SMILES	sFP1	sFP2	Class
1	SMILES1	1	1	cns
2	SMILES2	0	0	cns
3	SMILES3	1	0	Cardiovascular
3	SMILES4	1	0	Cardiovascular
4	SMILES5	1	1	cns
…	…	…	…	…
…	…	…	…	…



CART/binary-trees: Classification motivation



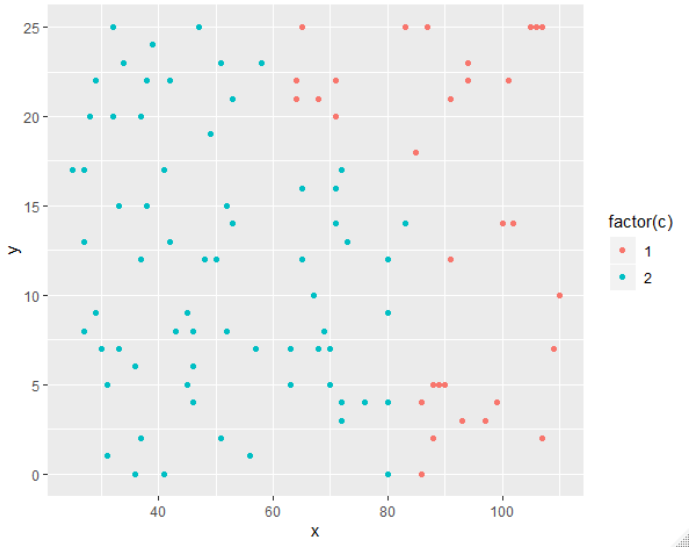


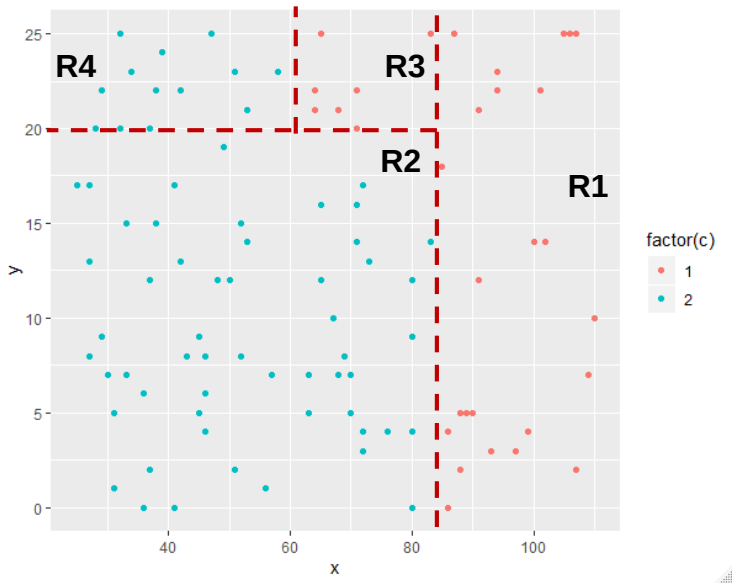
Split using single feature (x) and a cut-off (t_x >= 84)

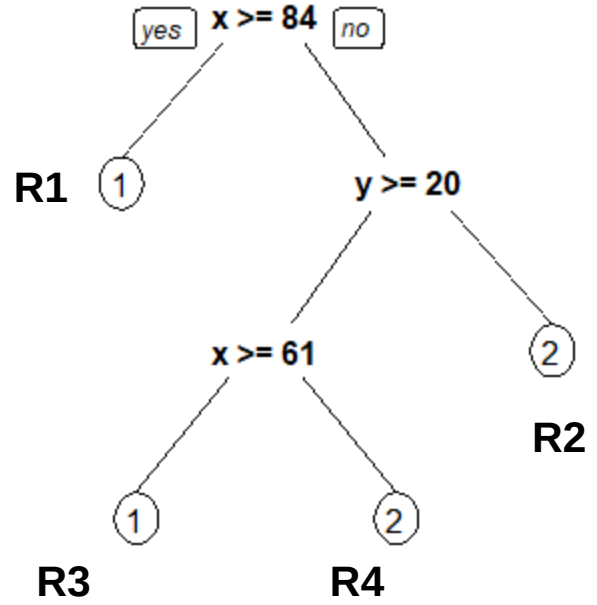
Choice of feature/cutoff is based on a COST function (that attempts of find pure nodes)

John Tukey (Box-plots)

Decision-trees: Classification motivation





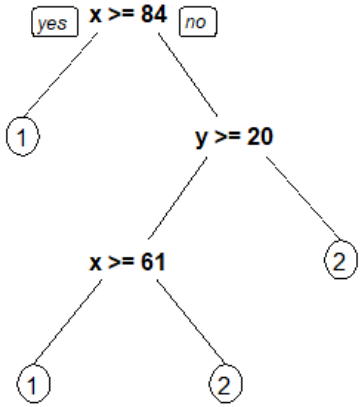


Terminal/Leaf nodes: R1, R2, R3
Internal nodes: Predictor space splitting points

CART produces binary tree; other algorithms (not common) can produce more than 2 children

Decision-trees: Important points

- Does trees explore all possible combinations
  - No? It uses something called **top-down**, **greedy** (best split at the particular step) approach; Not optimal but reasonably good
    - Recursive binary splitting

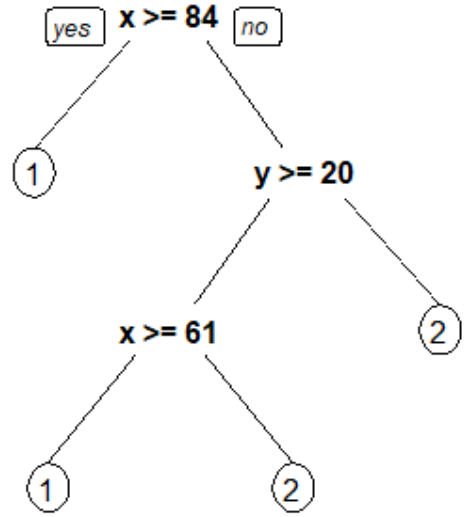


- Trees identify a predictor X_j and a cut-point c such that the splitting the predictor space leads to lower variance
  - Region1: **$\{X|X_j < c\}$;** Region2: **$\{X|X_j \geq c\}$**

- Tree splitting will continue from the above cut regions and will continue to split

Decision-trees: Important points

- Trees usually are grown bushier and pruned back to find a best sub-tree
  - Check Rob Tibshirani book or Google for details.



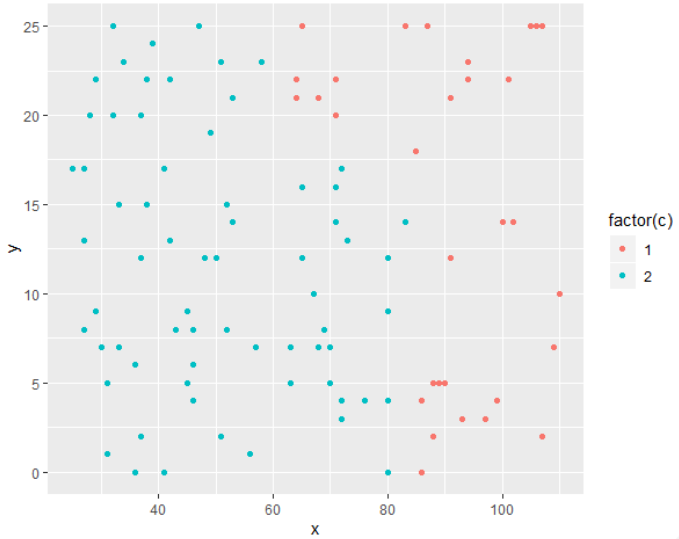
- Process will continue will our criteria is reached
  - We call this Hyperparameters
  - Bucket size, depth of tree etc.

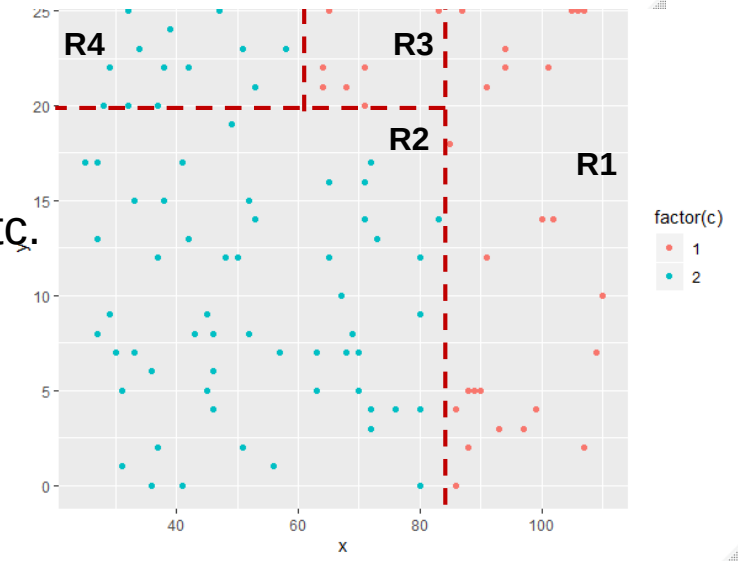
CANDLE (Cancer Distributed Learning Environment)

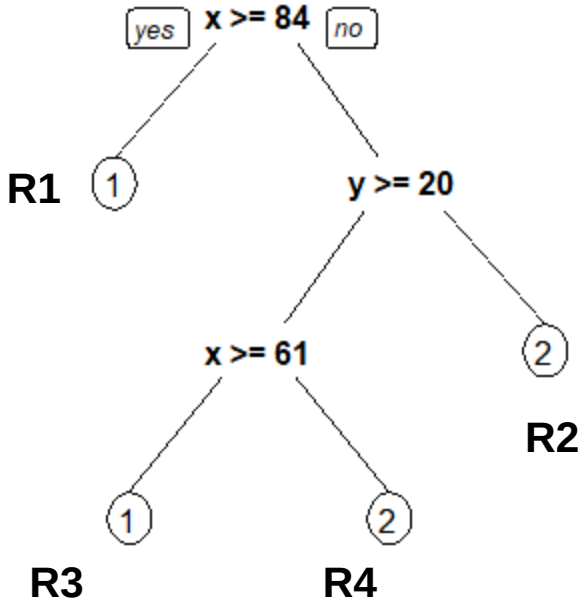
https://hpc.nih.gov/apps/candle/index.html

Hyperparameters

- Hyperparameters
  - Set before training a model
  - Drive the training process
  - Tuned between training iteration
- Examples
  - RandomForest
    - # of observations in a leaf etc.
  - KNN
    - Number of neighbors

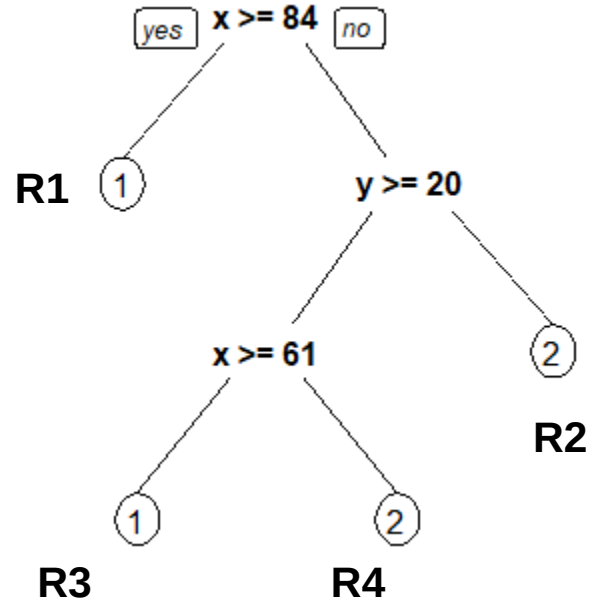






Decision-tree: Summary

- Outcomes: Categorical (unordered) variables
- Tree or decision tree is a set of **Yes/No** questions
- Predictions are given by the nodes (or ends)
  - That is which class is most common within the partition



- Trees work by partitioning/segmenting the predictor space (lines or boxes) with the hope of getting a pure space (ie of one class)

Tree building metrics: Measure of the quality of a split

- **Gini index** or node purity for a node, m
  - $G_m = \sum_{k=1}^{K} \hat{P}_{mk}\left(1 - \hat{P}_{mk}\right)$
    - mth region and kth class
  - A small value indicates a region that contains predominantly of one class
  - Pure node: G = 0; Mixed class node: G = 0.5 (equal proportions)

- **Cross-entropy** a similar measure to Gini index
  - $D = -\sum_{k=1}^{K} \hat{P}_{mk}\, log\left(\hat{P}_{mk}\right)$

Decision-Tree

- **Pros**:
  - Easy to explain
  - Interpretable
  - No preparation/scaling/centering
  - Non-linear method

- Cons
  - High variance
  - Unstable with small changes in the data
  - Perform poorly when compared to ensemble based methods (Random Forest)

Ensemble Methods: Random Forest

Law of Large Numbers

Wisdom of the crowd

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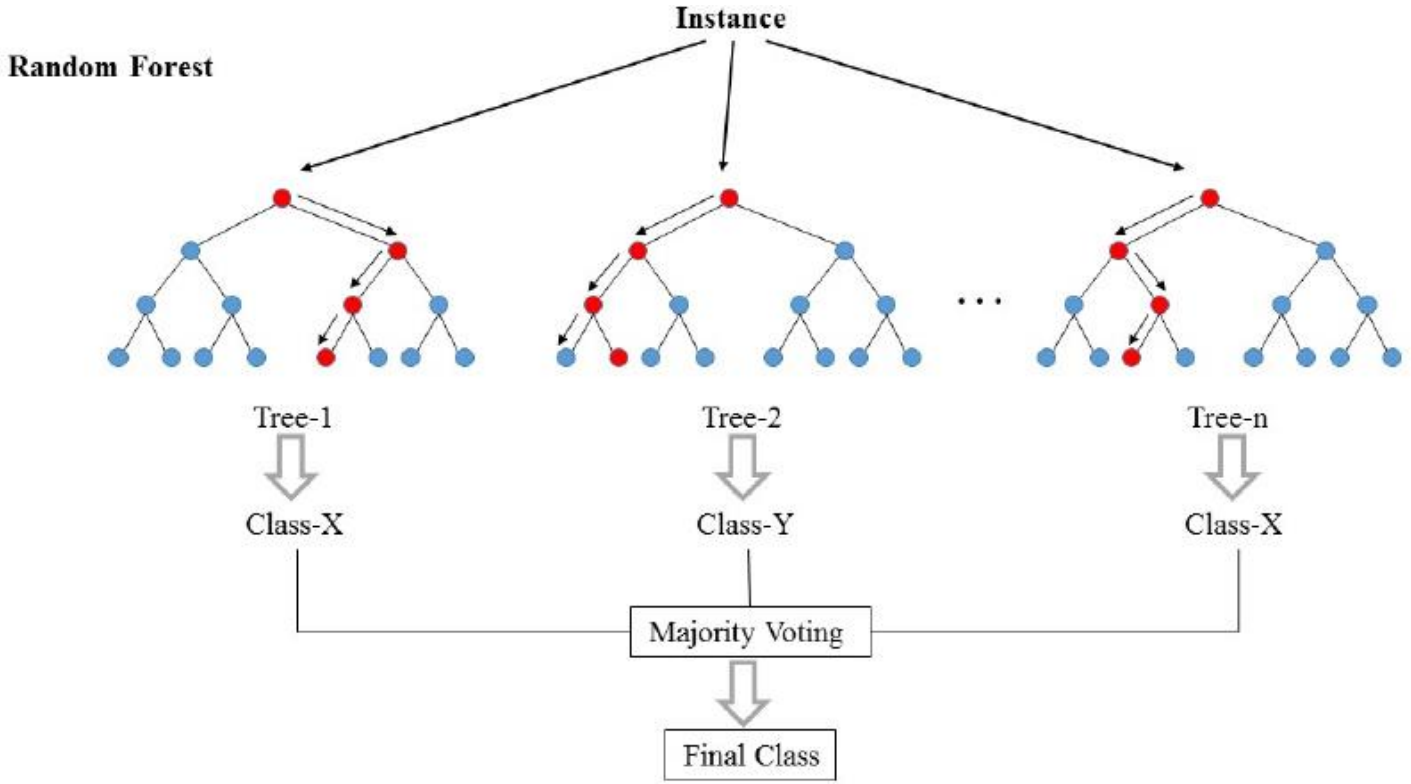

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For each observation, record the class prediction from each of the B trees and take a majority vote

Random Forest

- Combining a large number of trees result in improvements in accuracy
  - n independent measurements Z_1, …, Z_n each with variance of σ^2, variance of the mean $\bar{Z}$ will be $\frac{\sigma^2}{n}$

- Scikit-learn
  - Random sampling (with replacement; bootstrapping) of training data points when building trees
  - Random subsets
    - Usually $\sqrt{(n_\text{features})}$ considered when splitting nodes

Evaluation of binary classifiers

- Confusion Matrix and Balanced Accuracy (BA) Score
  - Count the number of times Class A is predicated as A or not (or other classes)

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{P}}$$

$$\mathrm{TNR} = \frac{\mathrm{TN}}{\mathrm{N}}$$

$$\mathrm{BA} = \frac{\mathrm{TPR} + \mathrm{TNR}}{2}$$

n = 1000	Predicted: Yes	Predicted:No	
Actual: Yes	890	10	900
Actual: No	90	10	100
	980	20	

Accuracy = 0.9000

TPR = 0.9082

TNR = 0.5000

BA = 0.7041

Overview of Classification Process

Training Data

Therapeutic Class Labels (MeSH Classification)

SMILES String of Drug Data

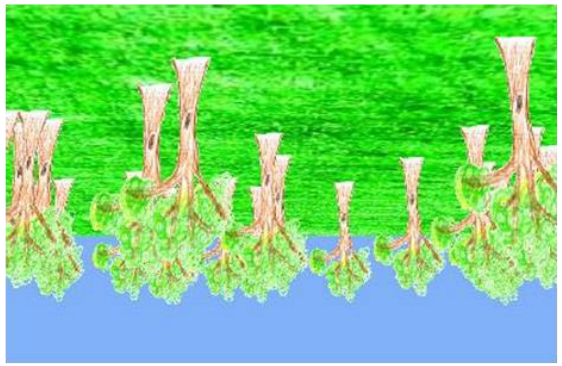
Fingerprints

1000010000.....10000010
1100010000.....00001010
0001010000.....11000010

Test Data

SMILES String of Drug Data

Random Forest



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- Respiratory System Agent
- Reproductive Control Agent
- Lipid Regulating Agent
- GI Agent
- Cardiovascular Agent
- Anti-neoplastic Agent
- CNS Agent
- Anti-infective Agent
- **Anti-inflammatory Agent**
- Dermatologic Agent
- Hematologic Agent
- Urological Agent

Thanks

- Contact Info
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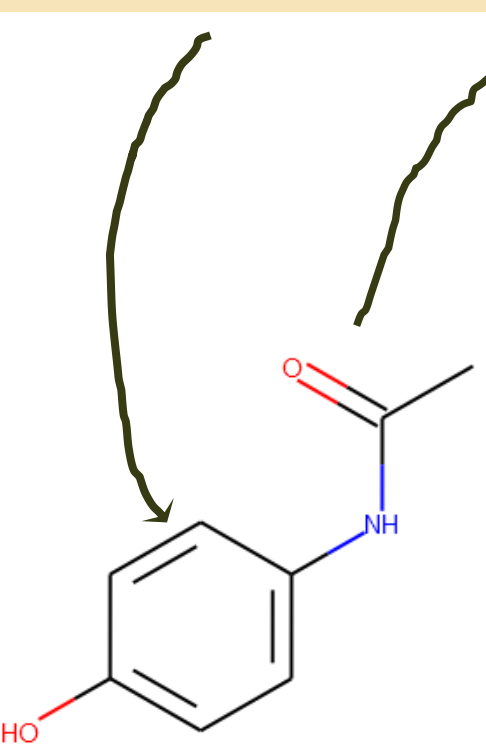
Extra

Evaluating Trees

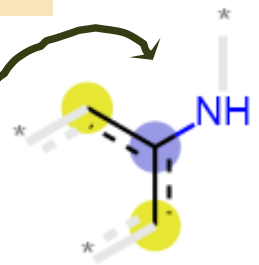
- Classification Error Rate
  - $E = 1 - \max_k(\hat{P}_{mk})$
  - $\hat{P}_{mk}$: proportion of training observations in the mth region that belong to kth class
  - But, this is not sensitive, noisy and not commonly used

SMILES → Structure → SubFragments → Fingerprint

CC(=O)NC1=CC=C(C=C1)O



Paracetamol



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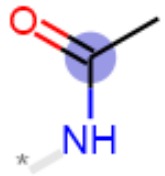

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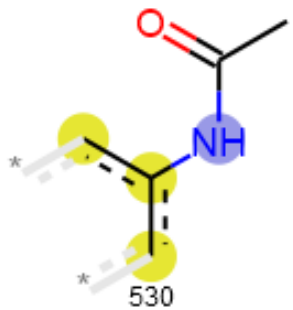

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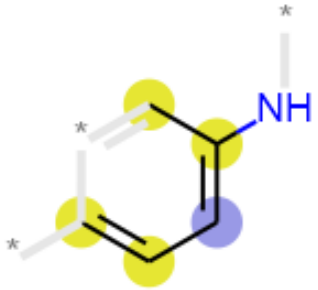

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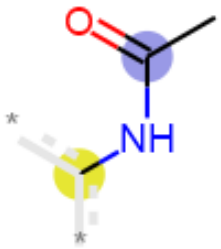

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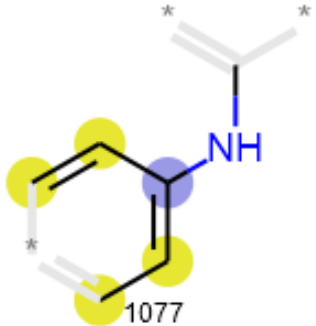

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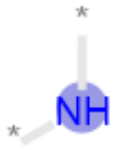
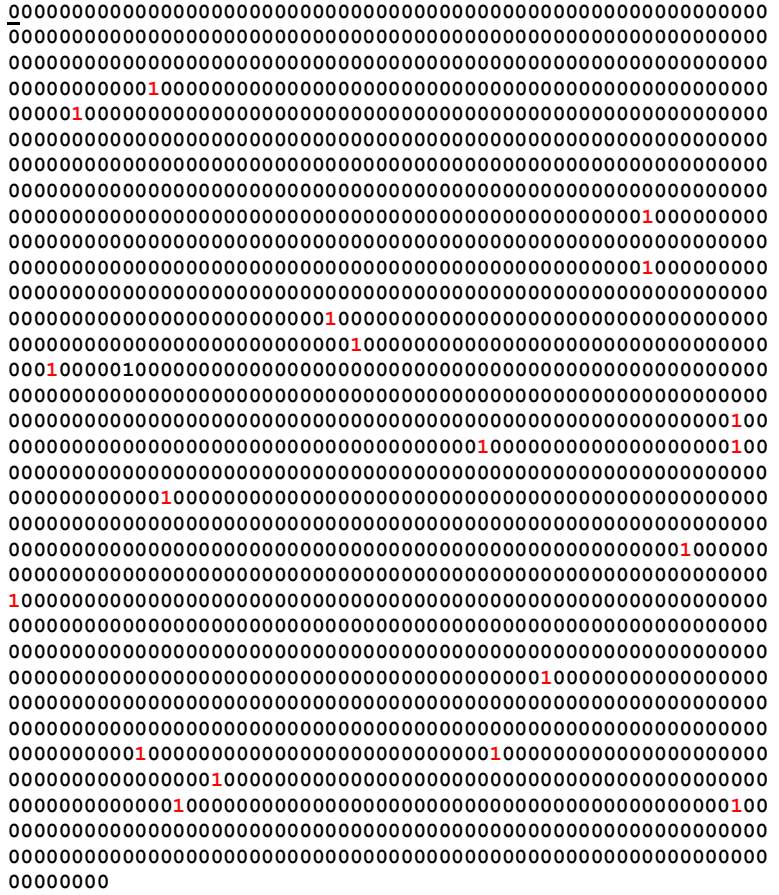
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