United States Environmental Protection Agency

Predicting Chromatography-tandem Mass Spectrometry Amenability to Improve Non-targeted Analysis

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United States Environmental Protection Agency

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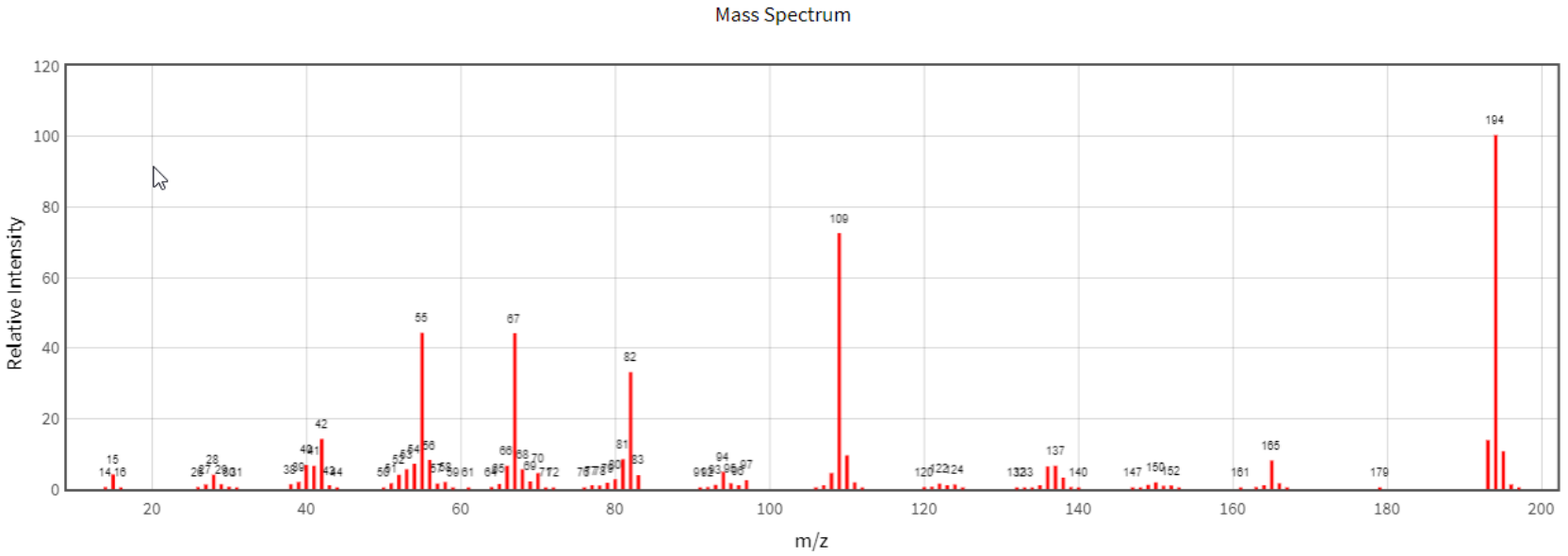
What are we trying to model?



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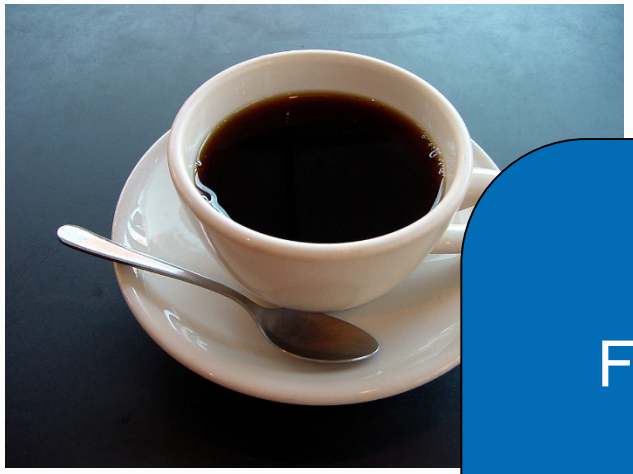
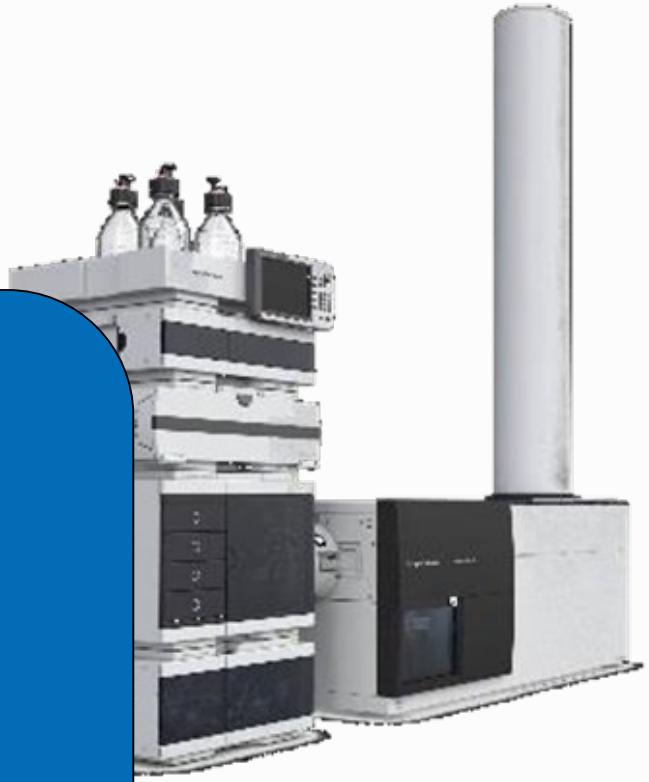
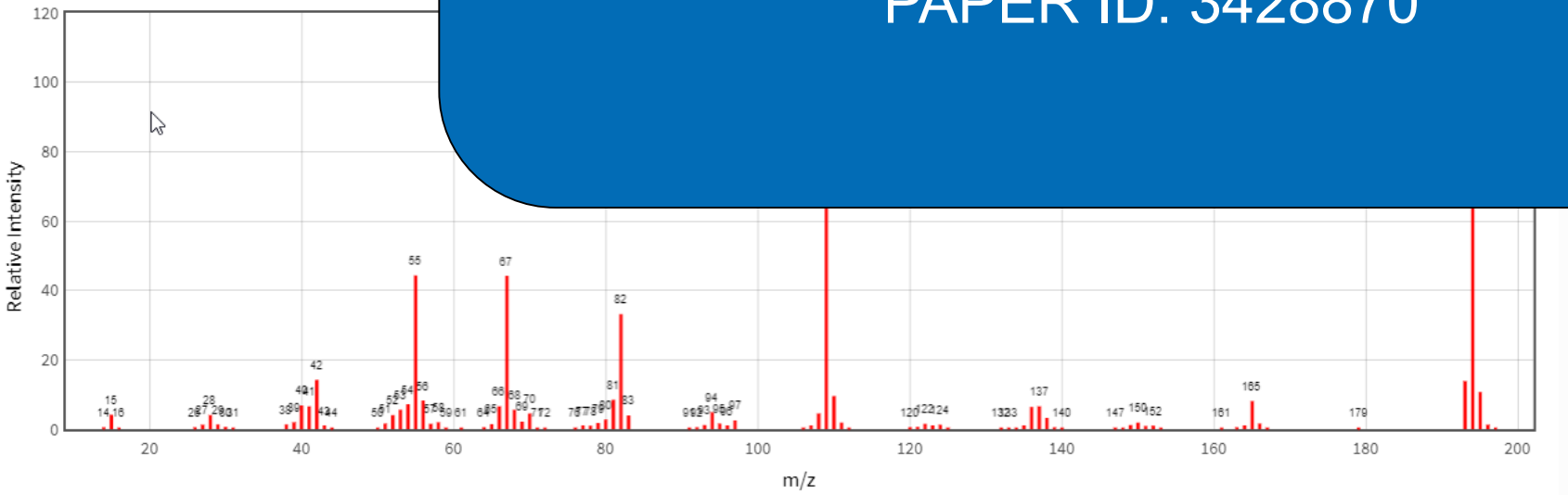
What are we trying to model?





For more details on NTA at EPA, please see:
EPA's research initiatives on non-targeted analyses of environmental chemicals
PRESENTER: Jon Sobus
PAPER ID: 3428870



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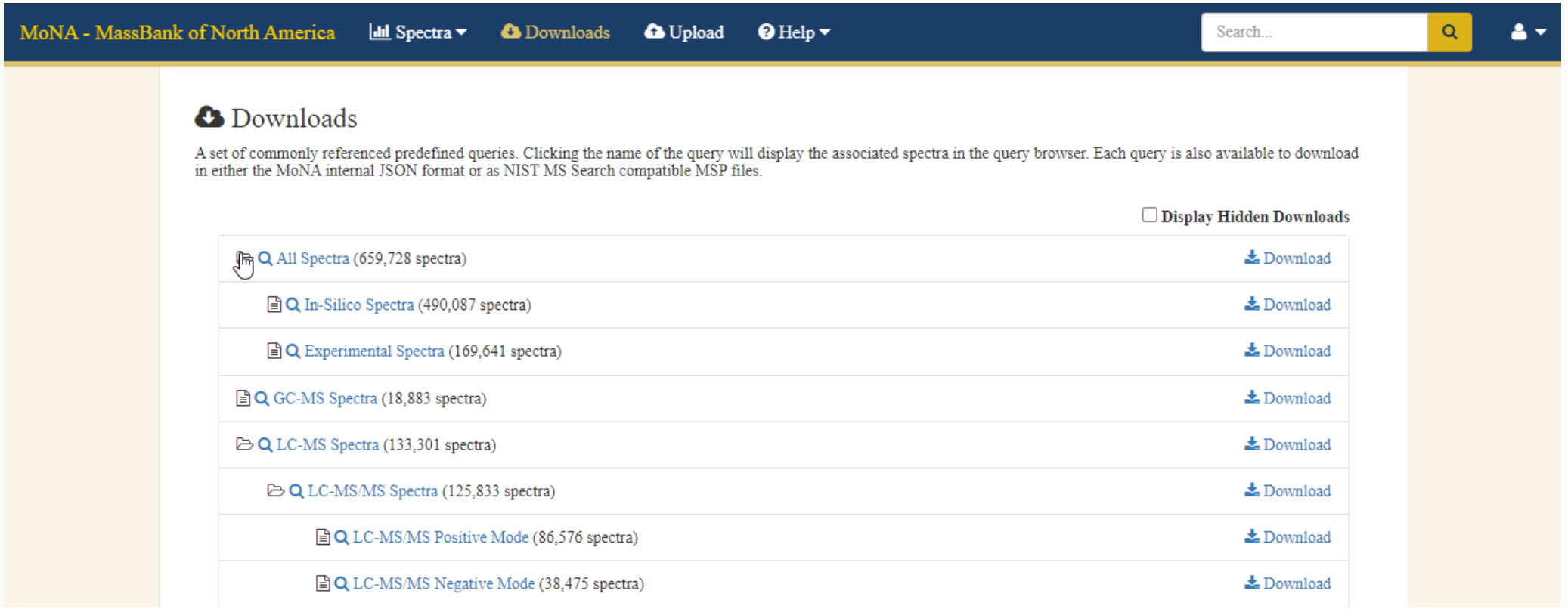
The more data, the better (most of the time..)

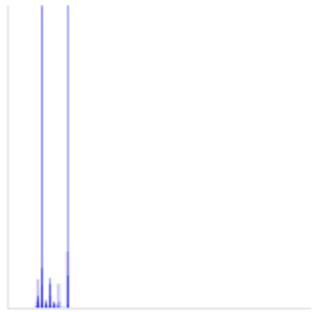


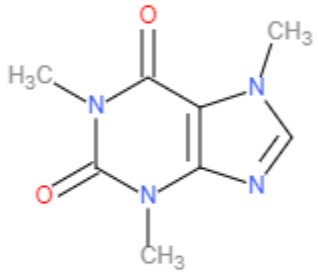
- 772 compounds in derivatized GCMS
- 7,199 compounds in non-derivatized GCMS
- **3,549 compounds in ESI+ LCMS**
- **2,630 compounds in ESI- LCMS**

EPA United States Environmental Protection Agency

Caffeine

Score: ★★★★☆



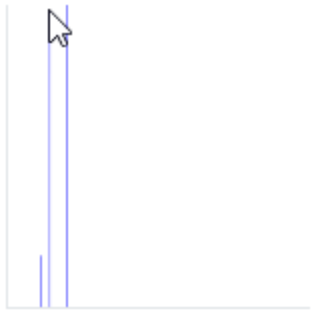


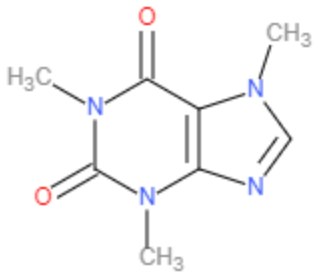
instrument	Pegasus III TOF-MS system...
instrument type	GC-EI-TOF
ms level	MS1
retention index	1880.2430
retention time	724.344 sec
ionization mode	positive
accession	OUF00133
date	2016.01.19 (Created 2010....
author	Tsujimoto Y, Tsugawa H, B...
license	CC BY-SA

Originally submitted to the MassBank High Quality Mass Spectral Database

Caffeine

Score: ★★★★☆

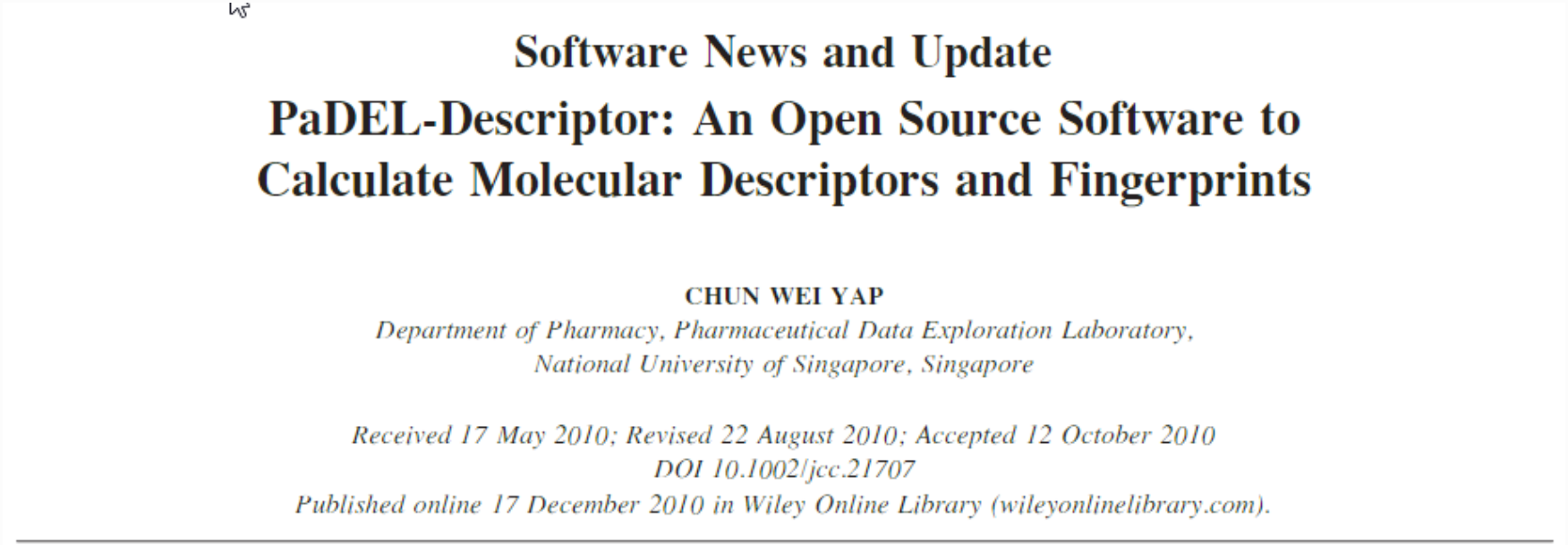




instrument type	QqQ
instrument	Micromass Quattromicro
collision energy	15eV
ionization	ESI
ionization mode	positive
ms level	MS2
precursor m/z	194.9000
precursor type	[M+H]+
accession	PM018511
publication	Alonso-Salces RM, Guillou...

Originally submitted to the RIKEN MS^n Spectral Database for Phytochemicals

Describing structures for modeling



Software News and Update

PaDEL-Descriptor: An Open Source Software to Calculate Molecular Descriptors and Fingerprints

CHUN WEI YAP
Department of Pharmacy, Pharmaceutical Data Exploration Laboratory, National University of Singapore, Singapore

Received 17 May 2010; Revised 22 August 2010; Accepted 12 October 2010
DOI 10.1002/jcc.21707
Published online 17 December 2010 in Wiley Online Library (wileyonlinelibrary.com).

- 1,444 1D & 2D Molecular descriptors from QSAR-ready SMILES. Examples include…
  - Electrotopological state
  - McGowan volume (van der Waals volume)
  - molecular linear free energy relationships
  - Atom, bond, & ring counts
  - LogP predictions, etc..

Reduction of descriptor space

Dimension reduction will improve our models and make calculations quicker

1. Remove any constant descriptors (variance(x) = 0)
2. Remove nearly constant descriptors (SD < 0.25)
   - 0.25 gives a good balance between reduction and retention
3. Calculate pair-wise correlations between remaining descriptors
   - Eliminate based on a cutoff = 0.96 correlation

1,444 descriptors → 385 descriptors

Datasets suitable for modeling

Models need both training and test data

- 75% of data for training, 25% for testing
  - Data stratified to maintain proportions in outcome variable
  - Different for each model
  - InChIKey skeleton as identifier
- External validation datasets
  - EPA's NTA Collaborative Trial (ENTACT) data (explicitly removed from train/test sets)

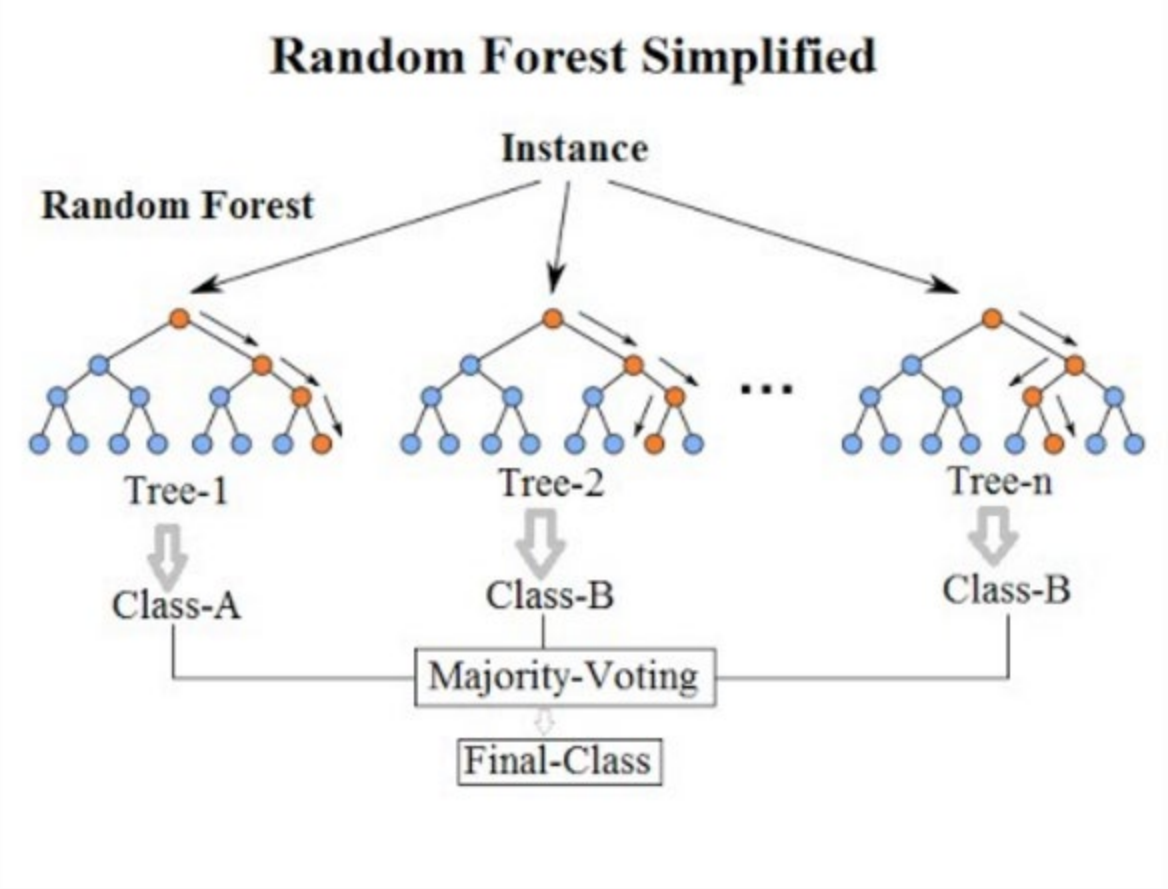
```
library(readxl)
library(caret)
library(randomForest)
library(funModeling)
library(tidyverse)
library(GA)
library(AdaSampling)
library(wsrf)
library(rsample)
library(dbscan)
```

R libraries used in study

Learning approach

- Four models
  - GC (derivatized), GC (not derivatized)

    ESI+ LC, **ESI- LC**
- Random forest (will explain)
  - Downsample absence data to match count of presence data
  - Optimize mtry and ntree via grid search
  - 5-fold cross validation
  - Y-randomization



Choosing the correct descriptors to predict the endpoint

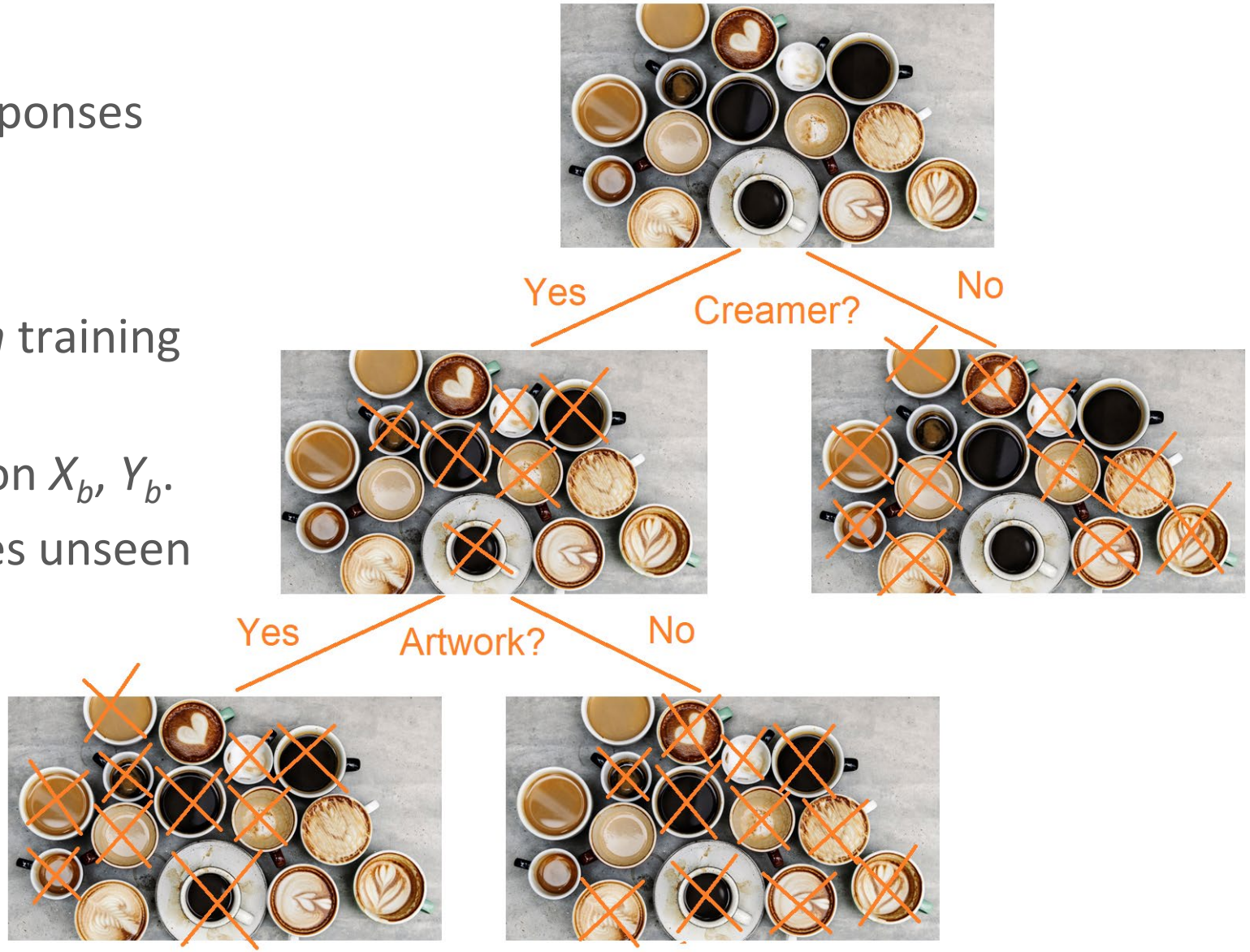
Random Forest Algorithm

Training set $X = x_1x_2...x_n$ with responses

$Y = y_1y_2...y_n$

For $b = 1,...,B$

1. Sample, with replacement, n training examples from X, Y; X_b, Y_b.
2. Train a classification tree f_b on X_b, Y_b.
3. The majority of all f_b classifies unseen samples.



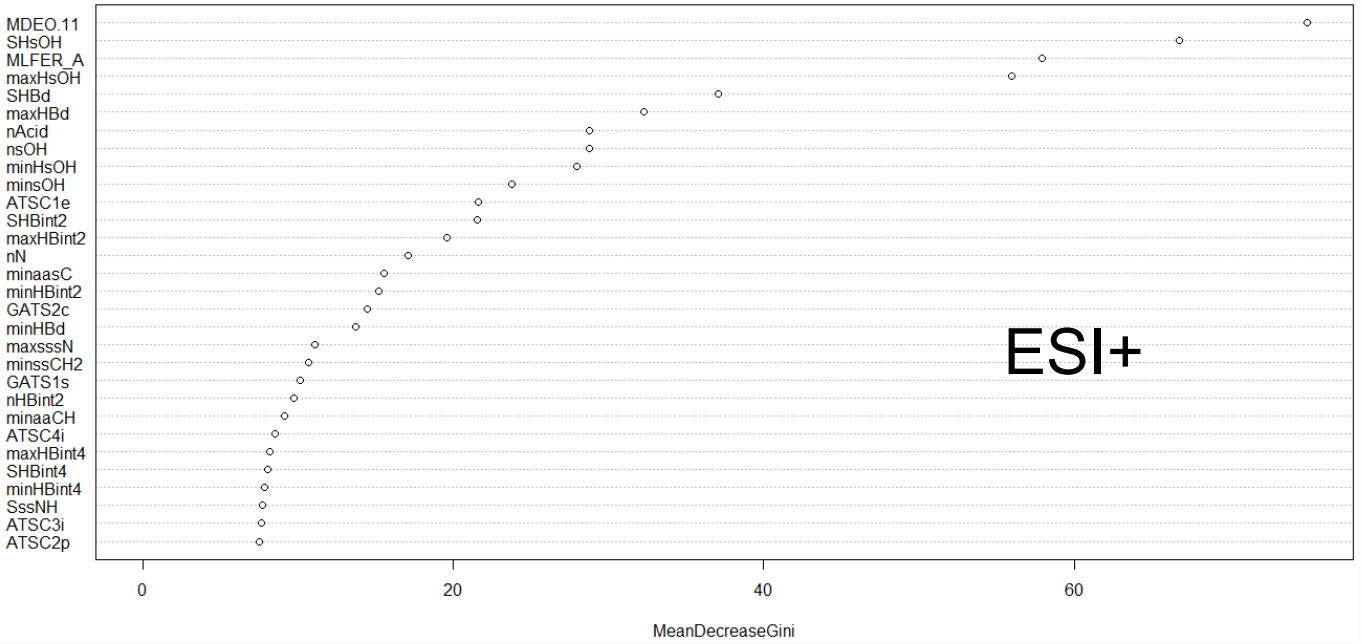
Negative data

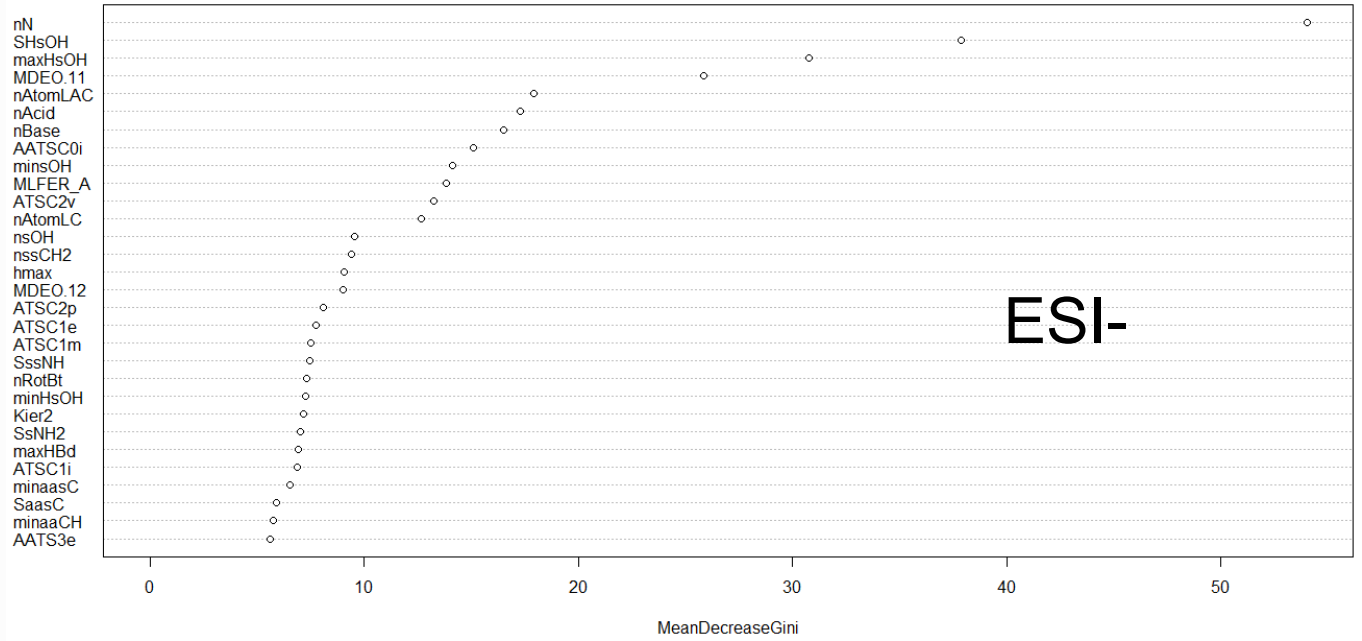
- Classification models need negative data, in addition to positive data
  - labs do not report chemicals NOT seen, only those identified by the instrument
- How do we provide a model with negative data?
  - produce the negative data ourselves (but note it is expensive)
  - assume all chemicals not present are absent
  - make assumption(s) as to what WAS tested
- For now, let's assume that if a chemical is detected in either ESI+/-, then it has also been tested in the other mode
- Still exploring reasonable assumptions for GCMS

Descriptor importance

Important descriptor descriptions

- MDEO-11
  - molecular distance edge between all primary oxygens
- MLFER-A
  - overall or summation solute hydrogen bond acidity
- SHsOH & maxHsOH
  - electrotopological state with respect to –OH fragments
- nN
  - the number of N atoms…





Model results

ESI+ Not Downsampled		
	Reference	
Prediction	Present	Absent
Present	2409	252
Absent	291	716
Sensitivity	0.8922	
Specificity	0.7397	
Balanced Accuracy	0.8159	

ESI+ Downsampled		
	Reference	
Prediction	Present	Absent
Present	2273	388
Absent	171	836
Sensitivity	0.9300	
Specificity	0.6830	
Balanced Accuracy	0.8065	

Model results

ESI- Not Downsampled		
	Reference	
Prediction	Present	Absent
Present	1659	305
Absent	291	1413
Sensitivity	0.8508	
Specificity	0.8225	
Balanced Accuracy	0.8366	

ESI- Downsampled		
	Reference	
Prediction	Present	Absent
Present	1649	315
Absent	271	1433
Sensitivity	0.8589	
Specificity	0.8198	
Balanced Accuracy	0.8393	

Internal test set results

ESI+ Not Downsampled		
	Reference	
Prediction	Present	Absent
Present	804	114
Absent	84	220
Sensitivity	0.9054	
Specificity	0.6587	
Balanced Accuracy	0.782	

ESI+ Downsampled		
	Reference	
Prediction	Present	Absent
Present	767	65
Absent	121	269
Sensitivity	0.8637	
Specificity	0.8054	
Balanced Accuracy	0.8346	

Internal test set results

ESI- Not Downsampled		
	Reference	
Prediction	Present	Absent
Present	551	104
Absent	115	452
Sensitivity	0.8273	
Specificity	0.8129	
Balanced Accuracy	0.8201	

ESI- Downsampled		
	Reference	
Prediction	Present	Absent
Present	545	92
Absent	121	464
Sensitivity	0.8183	
Specificity	0.8345	
Balanced Accuracy	0.8264	

Current & future work

- Comparing model results to ENTACT results
  - comparing predictions against independent labs, consensus of labs
- Considering new metrics for model quality
  - balanced accuracy not ideal when negative data may contain false negatives
- Applicability domains for models under development
  - global and local measures
- Working with collaborators to improve available data
  - data from additional potential collaborators would be GREATLY appreciated

Contributing researchers

EPA ORD

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Kristin Isaacs
Sarah Laughlin*
Jon Sobus
Kamel Mansouri*
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Elin Ulrich
John Wambaugh
Antony Williams

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Thank you for
Listening!

Questions?

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