Frederick National Laboratory
for Cancer Research

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ATOM Modeling Pipeline (AMPL) for Drug Discovery

S. Ravichandran,
Data Scientist, BIDS, FNLCR

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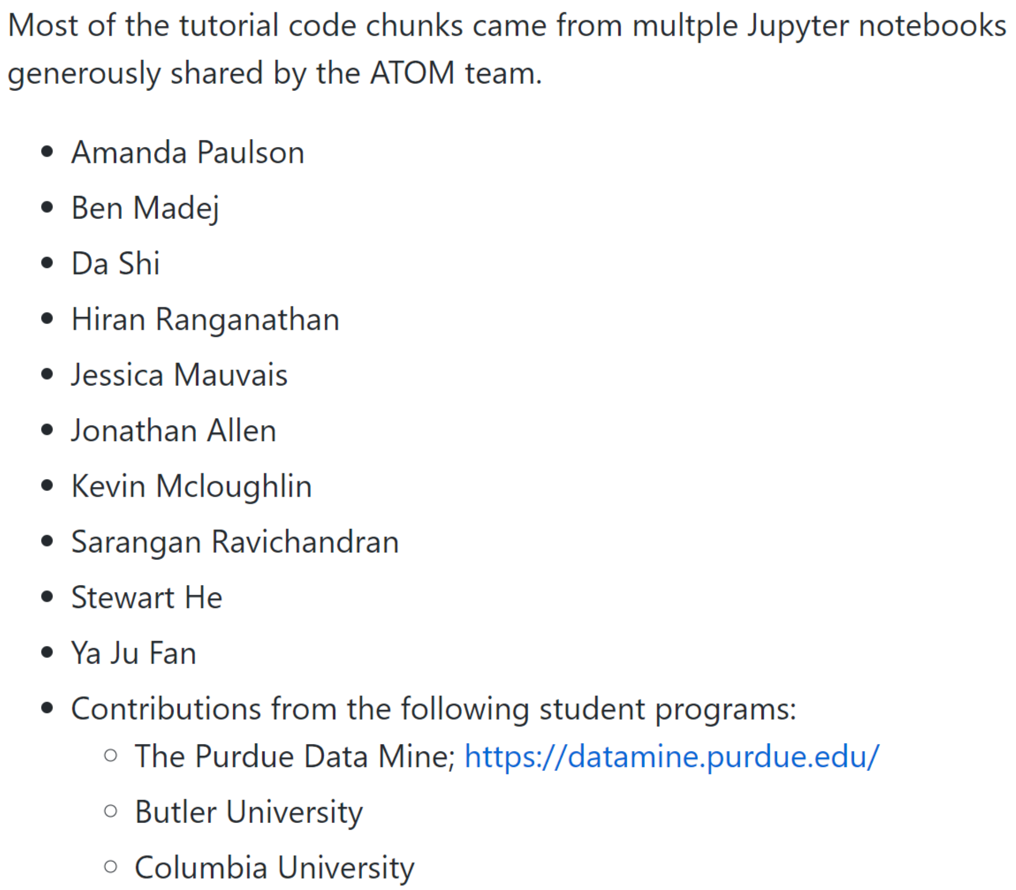
Acknowledgements

- ATOM Team

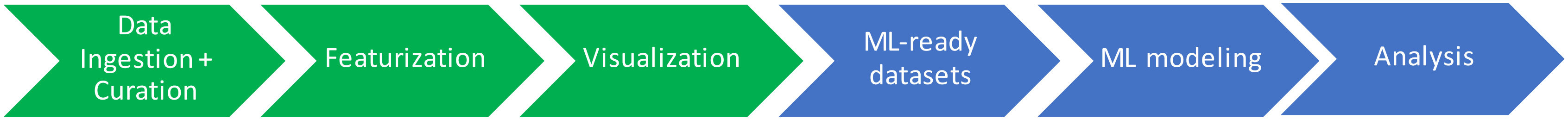


Most of the tutorial code chunks came from multple Jupyter notebooks generously shared by the ATOM team.

- Amanda Paulson
- Ben Madej
- Da Shi
- Hiran Ranganathan
- Jessica Mauvais
- Jonathan Allen
- Kevin Mcloughlin
- Sarangan Ravichandran
- Stewart He
- Ya Ju Fan
- Contributions from the following student programs:
  - The Purdue Data Mine; https://datamine.purdue.edu/
  - Butler University
  - Columbia University

Agenda

- Introduction to AMPL (ATOM Modeling Pipeline)
- Why AMPL?
- Goal for today



Data Ingestion + Curation

Featurization

Visualization

ML-ready datasets

ML modeling

Analysis

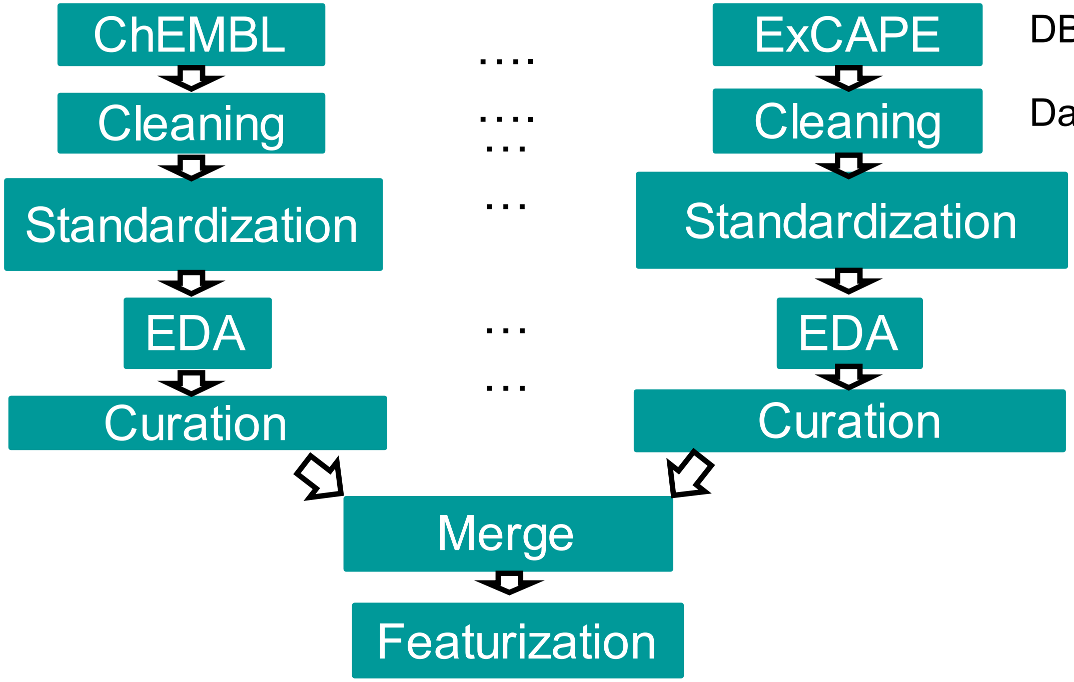
Data Sources

- ChEMBL: Manually curated repository of small molecules (EMBL/EBI)
  - ~1.9 M compounds; ~11K targets
  - https://www.ebi.ac.uk/chembl/
- ExCAPE-DB (EU program)
  - ~ 1M compounds/1.7K targets
  - https://solr.ideaconsult.net/search/excape/#
- Drug Target commons (Univ of Helsinki)
  - ~1.7M cpds; 13K targets
  - http://drugtargetcommons.fimm.fi/

Why combine data?

- ATOM team’s experience shows that the combined dataset (Union) models show robustness and performance than individual dataset

Overview



DB sources

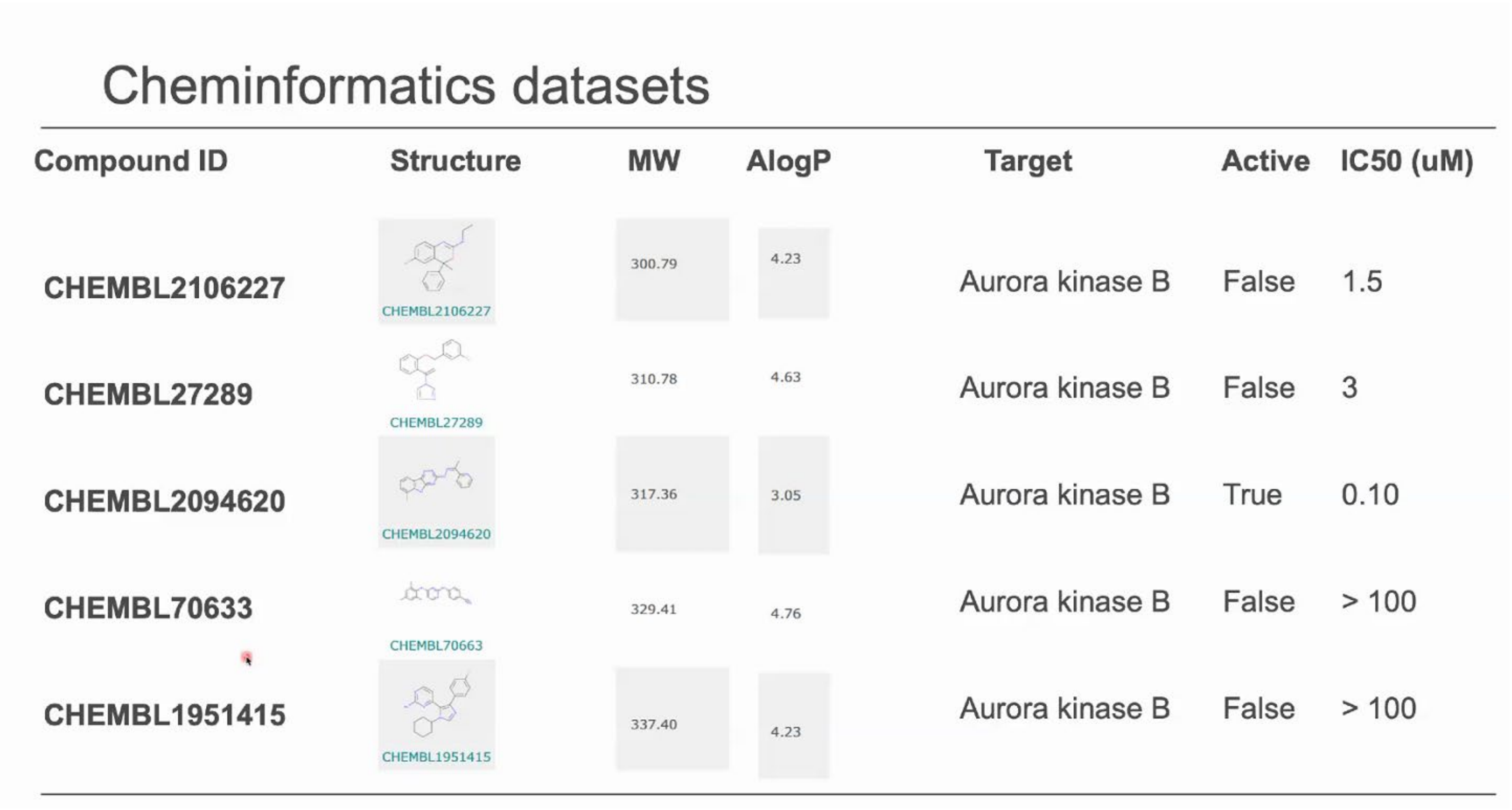
Data Tidying

base_smiles_from_smiles

diversity_plots*; heat map, tanimoto similarity*

Curate_data.aggregate_assay_data

A sample dataset



Cheminformatics datasets

Compound ID	Structure	MW	AlogP	Target	Active	IC50 (uM)
CHEMBL2106227	CHEMBL2106227	300.79	4.23	Aurora kinase B	False	1.5
CHEMBL27289	CHEMBL27289	310.78	4.63	Aurora kinase B	False	3
CHEMBL2094620	CHEMBL2094620	317.36	3.05	Aurora kinase B	True	0.10
CHEMBL70633	CHEMBL70663	329.41	4.76	Aurora kinase B	False	> 100
CHEMBL1951415	CHEMBL1951415	337.40	4.23	Aurora kinase B	False	> 100

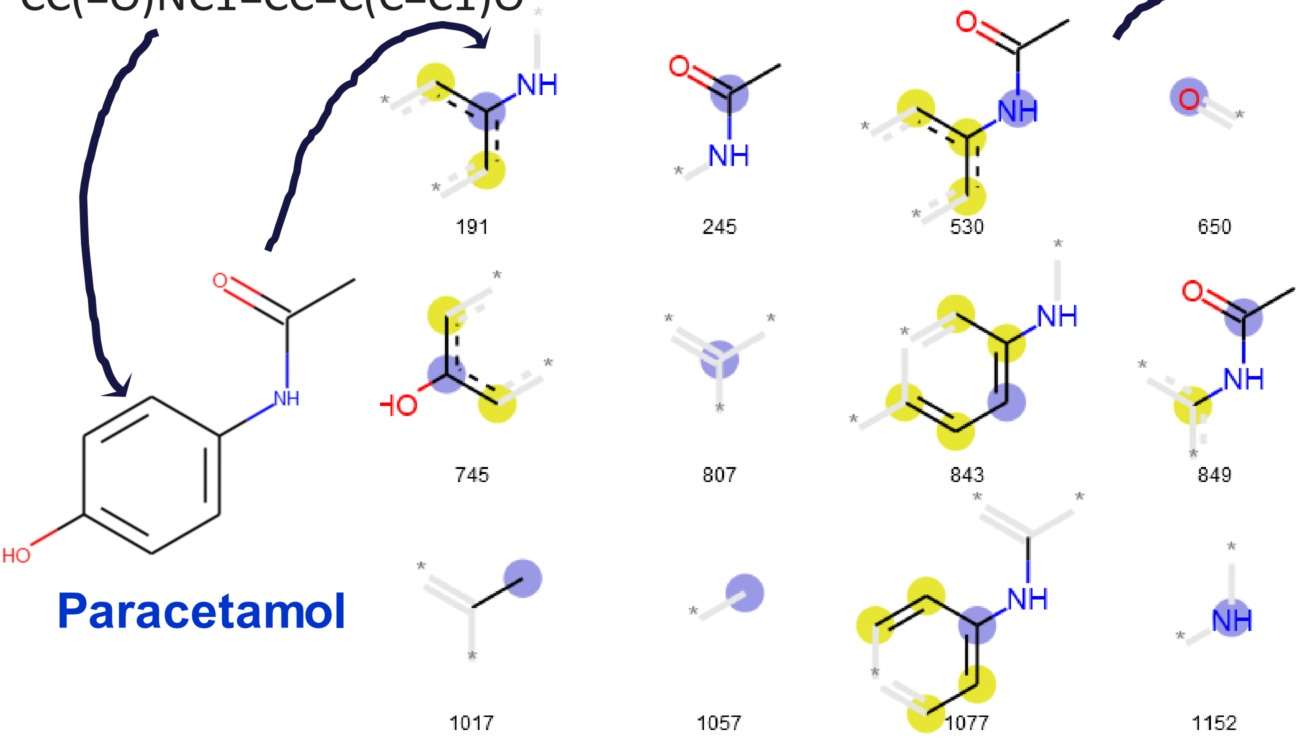
Featurizing a molecule: Fingerprints

- Fingerprints
  - Molecules → fixed-length binary vectors (0s and 1s). indicating presence/absence of certain molecular features
  - One can compare fingerprints of two molecules and identify similarity

		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
…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…

SMILES → Fingerprint

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



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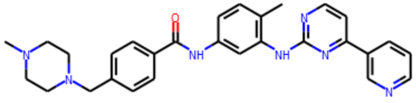
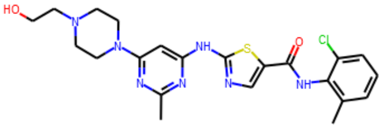
Featurizing a molecule: Molecular descriptors

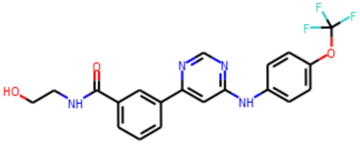
- Physicochemical properties
  - Molecular weight, # of Hydrogen bond donors, log partition coefficient etc.
- Mordred
  - ~1800 descriptors
  - Open source software
  - Implemented in AMPL



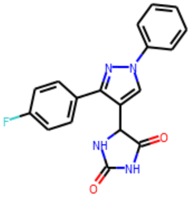
Imatinib



Dasatinib



GNF



DPH

	ABC	ABCGG	nAcid	nBase	SpAbs_A	SpMax_A	SpDiam_A	SpAD_A	SpMAD_A	LogEE_A	...	SRW10
0	29.198227	19.516970	0	2	49.161634	2.372244	4.744487	49.161634	1.328693	4.541483	...	10.415502
1	25.731643	19.151718	0	1	42.312870	2.394767	4.762938	42.312870	1.282208	4.422390	...	10.323283
2	23.132682	16.941805	0	0	38.063201	2.370962	4.741923	38.063201	1.268773	4.312334	...	10.143881
3	19.924959	16.140292	0	0	32.867760	2.498596	4.828813	32.867760	1.314710	4.170130	...	10.150621

https://mordred-descriptor.github.io/documentation/master/descriptors.html

Computing Environment

BIOWULF

HIGH PERFORMANCE COMPUTING AT THE NIH

COLAB	NIH HPC Biowulf
Serverless	Can ask for resources
Resources are !unlimited and !guaranteed	Resources are guaranteed
Browser-based	Mostly command-line
Good for short jobs; explaining AMPL capabilities	Long jobs (HPO)
Audience: Interns, Workshop attendee (Educational)	Research

Curation

- Data Curation
  - Organization and integration of data from multiple sources
- Potent Targets
  - Dose-response measurements (Kd, Ki, IC50 and activity) in biochemical assays
    - <= 100 nM
  - Dose response measurements (activity %, % inhibition etc)
    - Different cutoffs for biochemical and cell-based assays
  - Multiple assays (different studies or data resources)
    - Median bioactivity
- Mutation data

Modeling Steps

- Data cleaning, tidying
- Data curation
- Feature engineering
  - Outcome variable IC50 → pIC50
  - Numerical → categorical
- EDA
  - FP → Tonimoto → tSNE
- Aggregate assay
- Diversity plots
- Featurization

Bio-assay with a specific target protein

- Identifying drugs or compounds primary targets and off-targets is a critical task in drug discovery
  - Kinases
    - Target promiscuity → polypharmacological effects
- Understanding this concept can help us with the drug repurposing efforts
- Many groups collect and curate Target-drug data
  - Diversity of experiments
    - Different bioassay, bioactivity endpoints etc. makes the problem challenging

Useful links

- https://github.com/ATOMconsortium/AMPL
- https://github.com/ravichas/AMPL-workshop-1
- https://github.com/ATOMconsortium/AMPL/tree/Tutorials/atomsci/ddm/examples/tutorials
- https://hpc.nih.gov/apps/ampl.html

- Workshop materials
- https://github.com/ravichas/AMPL-workshop-1