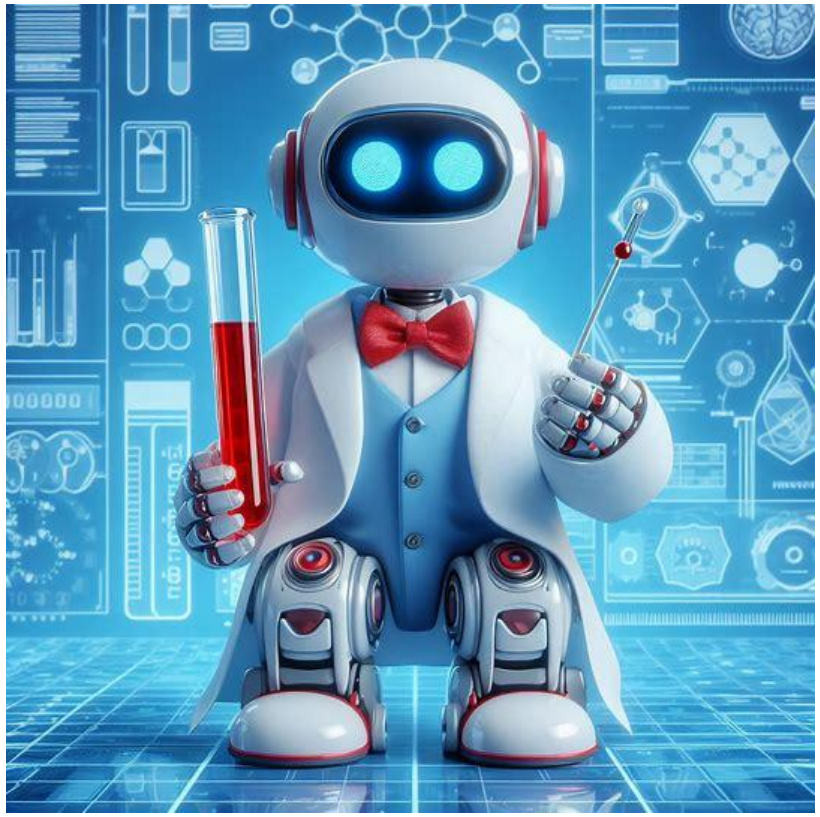


# AI in Drug Discovery – An Overview

Andrea Volkamer and Pat Walters

September 16, 2024

## Session 2 - Data is all you need!

# Who we are!

**Pat Walters**
**OpenADMET**

**Raquel López-Ríos de Castro**
**Saarland University**

**Afnan Sultan**
**Saarland University**

**Lisa-Marie Rolli**
**Saarland University**

**Andrea Volkamer**
**Saarland University**

# What we will do today

## Session 1 - 1:30 - 2:30 pm

- An introduction to Artificial Intelligence (AI) and Machine Learning (ML)
- Molecular representations
- AI architectures

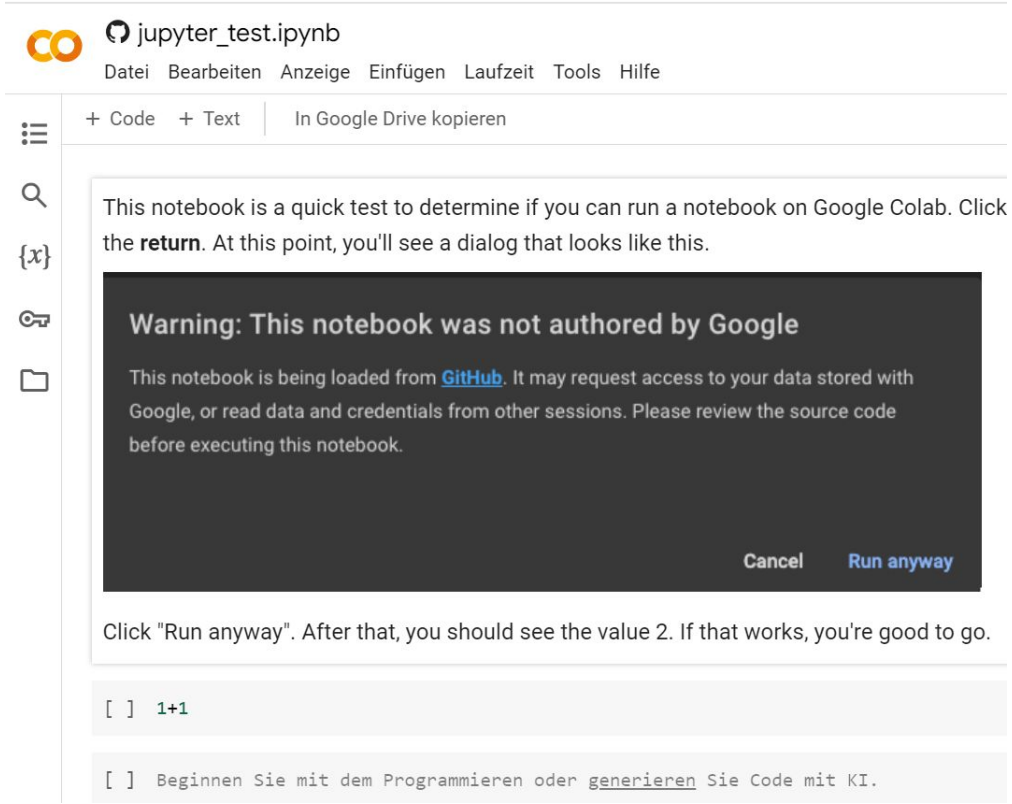
## Session 2 - 3:00 - 4:00 pm

- Importance of data quality for AI and ML
- Data (pre)processing
- Exploratory data analysis
- Applicability domains

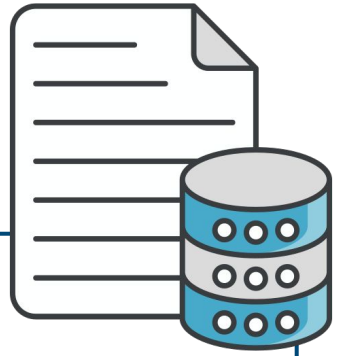
## Session 3 - 4:30 - 5:30 pm

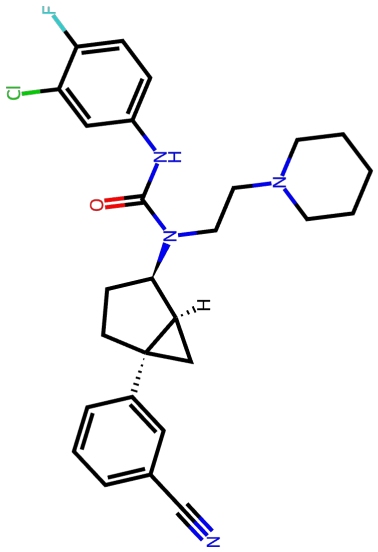
- AI in practice
- Molecule generation
- Active learning

Lectures supported by hands-on sessions …



# The Path From Molecules to Properties

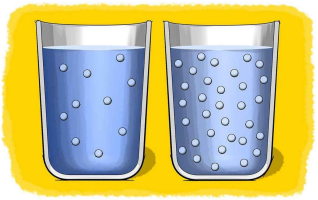


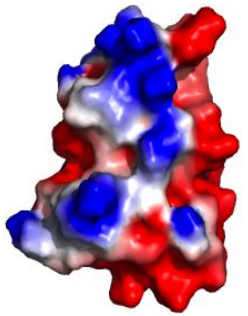


## Supervised Learning (SL)

**Representation**
- Physchem properties
- Morgan FPs
- Adjacency matrix

**Model**
- RF
- SVM
- GNN





## Self-Supervised Learning (SSL)

**Tokenization**
- Sequences
- Graphs

**Foundational Models**
- Transformers
- Autoencoders

**Fine-tuning**

# The Two Limiting Factors

Data

∞

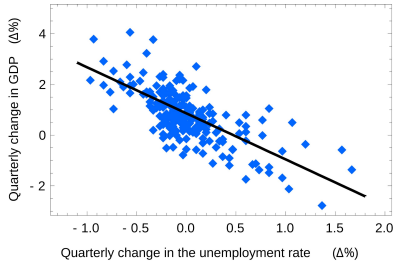
Limited

Representative

*Just* needs the right model!

Model

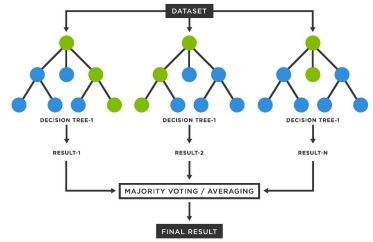
Simple




$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \ldots + \epsilon$$

$$P = N_{features} + 2$$

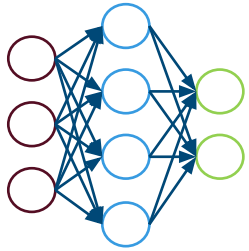
Moderate




$$Y = \frac{1}{T}\sum_{t=1}^{T} f_T(x)$$

$$P \propto N_{trees}, T_{depth}, \ldots$$

Complex



$$Y^l = W^l a^{l-1} + b^l$$

$$P \propto W, b$$

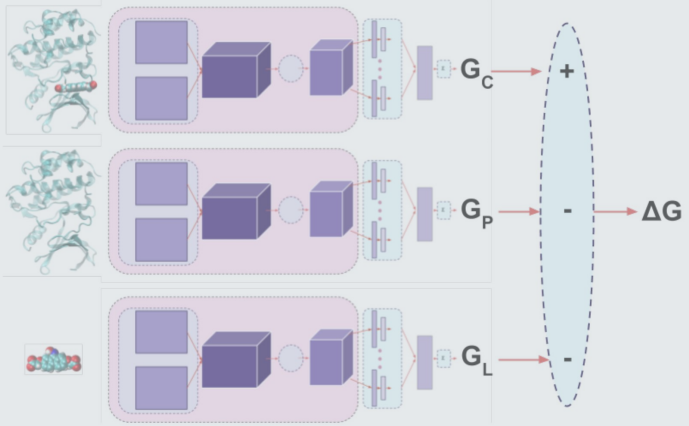
P = # parameter

# Key Components of Machine Learning in Drug Discovery (or Anything Else)

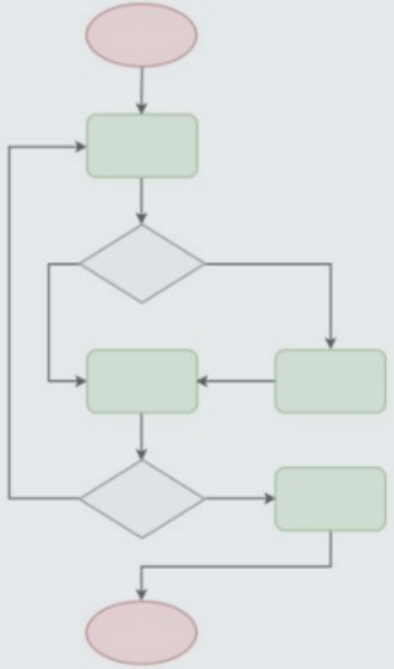
## Data

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.0009 | 0.004 | 0.0008 | | | | 26.7 | 4.2 | | 0.232 | | |
| 0.001 | 0.004 | 0.0016 | | | | 16.2 | 5.2 | | 0.179 | | |
| 0.001 | 0.734 | 0.0076 | | | | | | | | | |
| 0.001 | 0.034 | 0.003 | | | | 17.5 | 3.5 | | 0.262 | | |
| 0.001 | 0.017 | 0.0014 | <1.0 | | | 30.5 | 3.8 | | 1.4 | | |
| 0.0015 | 3.645 | 0.0415 | 36.9 | | | | | | 12 | | |
| 0.002 | 3.92 | 0.028 | 185.2 | | | 30 | 2.5 | | 0.583 | | |
| 0.001 | 0.1965 | 0.004 | 198.7 | | | 24.4 | 3.5 | | 3.1 | | |
| 0.0006 | 0.1886 | 0.0026 | 126.5 | 34 | 5.2 | 70.4 | 3.2 | 49.6 | 9.15 | 0.25 | 0.231 |
| 0.001 | 0.0145 | 0.003 | 4.1 | | | 26.2 | 3.5 | | 1.3 | | |
| 0.001 | 1.259 | 0.0048 | 9.3 | | | | | | 2.2 | | |
| 0.001 | 0.007 | 0.0026 | 173.0 | | | 12.5 | 1.4 | | 0.395 | | |
| 0.0016 | 0.73133 | 0.0063 | 8.9 | 186.9 | 4.3 | 72.1 | 3.8 | 7.3 | 14.45 | 1 | 7.4 |
| 0.001 | 0.007 | 0.0008 | 137.0 | | | 26.8 | 3.9 | | 5 | | |
| 0.0006 | 0.0075 | 0.0008 | 56.2 | | | | | | 0.218 | | |
| 0.001 | 0.0095 | 0.002 | | | | 5.9 | 4.3 | | 3.1 | | |
| 0.0035 | 14.885 | 0.121 | | | | | | | | | |
| 0.0026 | 0.054667 | 0.0305 | ---v--- | 47.7 | 4 | 17.1 | 4.5 | 19.4 | 2.4 | 2 | 0.696 |
| 0.0007 | 0.006 | 0.004 | ---v--- | | | 21.6 | 16.7 | | 6 | | |
| 0.001 | 0.533 | 0.0083 | ---v--- | | | 53.6 | 5.3 | | 7.5 | | |
| 0.001 | 0.207 | 0.026 | ---v--- | | | 0.498 | 6.2 | | 30 | | |
| 0.001 | 0.2755 | 0.0043 | ---v--- | | | | | | 0.397 | | |
| 0.001 | 0.3525 | 0.006 | ---v--- | | | | | | 0.367 | | |

## Representation




## Algorithms



# Where Machine Learning Excels ⟷ Pharmaceutical Data Properties

**(Ultra)Large amounts of data**
- Pharmaceutical data is miniscule compared to many other fields

**Responses are definitive**

**Samples are independently distributed**
- No cases where the same example falls into 2 different categories

**Samples are identically distributed**
- Equal distributions of positive and negative examples

**Training data is representative of what is being predicted**

**Data is sparse**
- Rarely have a complete data matrix

**Data is truncated**
- Many assay values report as “<1” or “>30”
- Difficult to know the true value

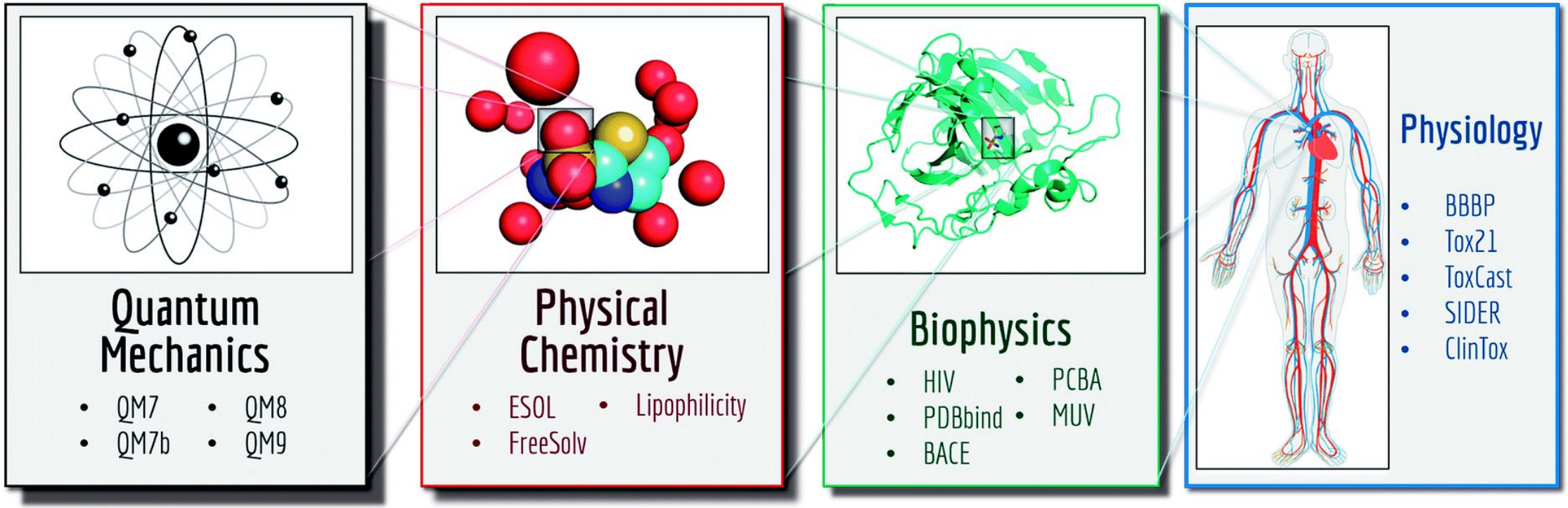
**Data has a limited dynamic range**
- Often spans only 2 or 3 logs
- Small dynamic range combined with experimental error makes significant correlations difficult

**Even data from the “same” assay can be heterogeneous**
- PK data measured with different doses, formulations
- Response can vary with operator, equipment, lab

**Data covers a limited chemical space**
- Even global models can be local

# Small Molecule Benchmark Datasets: MoleculeNet

**Common molecule benchmarks for molecular property prediction:**
16 datasets divided into 4 categories.




https://moleculenet.org/

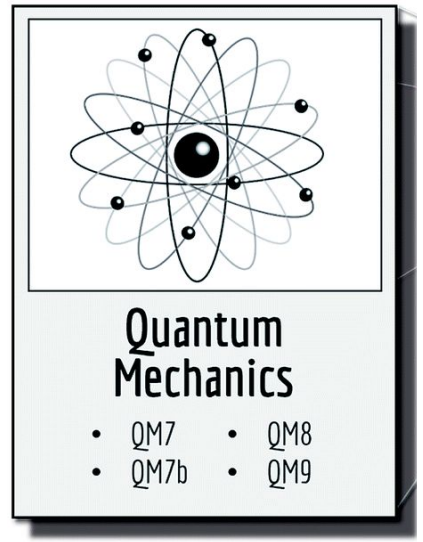
# Small Molecule Benchmark Datasets: e.g., QM9 and Tox21

**Quantum Mechanics data: QM9 → regression tasks**

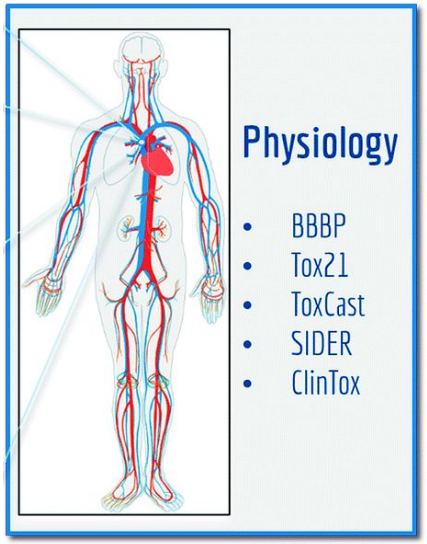
- ~134k molecules (SMILES, 3D) with <= 9 heavy atoms
- 12 properties: Geometric, energetic, electronic, and thermodynamic properties of DFT-modelled small molecules
- Commonly used due to its comparably large size

**Tox21 → classification**

- Toxicity data with molecules measured against toxicity-relevant endpoints
- ~8k molecules
- 12 tasks, here biological targets, including nuclear receptors and stress response pathways




https://moleculenet.org/




**CAREFUL! See Pat's BlogPost**
https://practicalcheminformatics.blogspot.com/2023/08/**we-need-better-benchmarks-for-machine**.html

# Benchmark Data Sets: Therapeutic Data Commons (TDC)

Check for updates

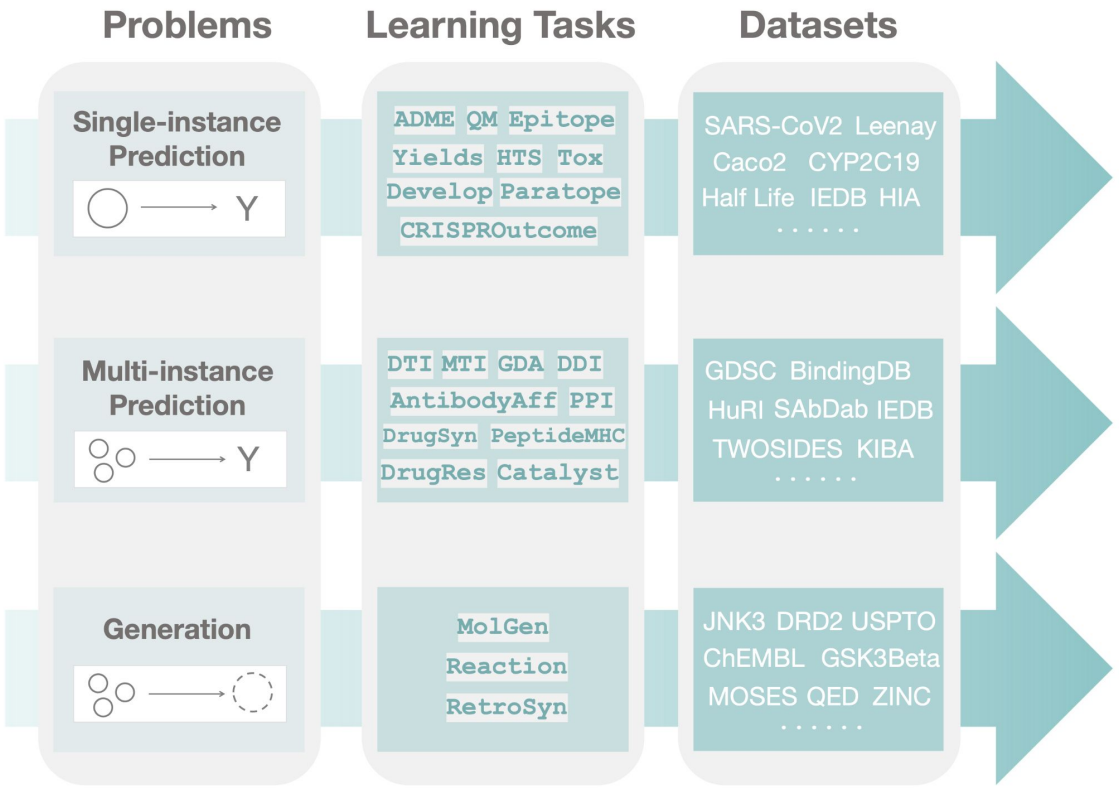
comment

## Artificial intelligence foundation for therapeutic science

Artificial intelligence (AI) is poised to transform therapeutic science. Therapeutics Data Commons is an initiative to access and evaluate AI capability across therapeutic modalities and stages of discovery, establishing a foundation for understanding which AI methods are most suitable and why.

Kexin Huang, Tianfan Fu, Wenhao Gao, Yue Zhao, Yusuf Roohani, Jure Leskovec, Connor W. Coley, Cao Xiao, Jimeng Sun and Marinka Zitnik

Nat Chem Biol (2022). https://doi.org/10.1038/s41589-022-01131-2

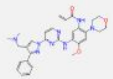
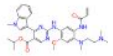
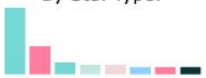
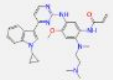



**CAREFUL! See Pat's BlogPost**

https://practicalcheminformatics.blogspot.com/2023/08/**we-need-better-benchmarks-for-machine**.html

# Small Molecule Bioactivity Datasets: ChEMBL or PubChem

## Database for collecting binding affinities

| ChEMBL ID | Search Hit | Name | Synonyms | Type | Max Phase | Molecular Weight | Targets | Bioactivities |
|---|---|---|---|---|---|---|---|---|
|  CHEMBL4558324 | | LAZERTINIB | C-18112003-G, GNS1480, GNS-1480, JNJ-73841937-AAA, Lazertinib, Yh25448, YH25448, YH-25448 | Small molecule | 3 | 554.66 | 12 By Type:  | 44 By Std. Type:  |
|  CHEMBL4650319 | | MOBOCERTINIB | AP32788, AP-32788, Mobocertinib, Tak-788, TAK-788 | Small molecule | 4 | 585.71 | 14 By Type:  | 55 By Std. Type:  |
|  CHEMBL4761468 | | AUMOLERTINIB | Almonertinib, Ameile, Amerol, Aumolertinib, Egfr t790m inhibitor hs-10296, EQ143, EQ-143, HS-10206, Hs 10296, Hs-10296, HS-10296 | Small molecule | 3 | 525.66 | 5 By Type:  | 23 By Std. Type:  |


https://www.ebi.ac.uk/chembl/

# Recommended Datasets Supplied By the Polaris Initiative

https://polarishub.io/datasets?certifiedOnly=true


Polaris certified datasets have been evaluated and approved by industry experts

# Small Molecule Datasets (unlabelled): ZINC and GuacaMol

**ZINC (https://pubs.acs.org/doi/full/10.1021/acs.jcim.5b00559)**

- Ultralarge collection of purchasable, "drug-like" molecules without target value
- ZINC15: ~120M molecules
- ZINC20: ~1.4 billion molecules,

**GuacaMol (https://pubs.acs.org/doi/10.1021/acs.jcim.8b00839)**

- Large collection of molecules from ChEMBL 24 without target value
- ~1.5M molecules
- Published training, test and validation set → for benchmarking

➔ **Commonly used benchmark for pretraining (LLMs) and generative models**

# (Benchmark) Data Quality – Technical Issues

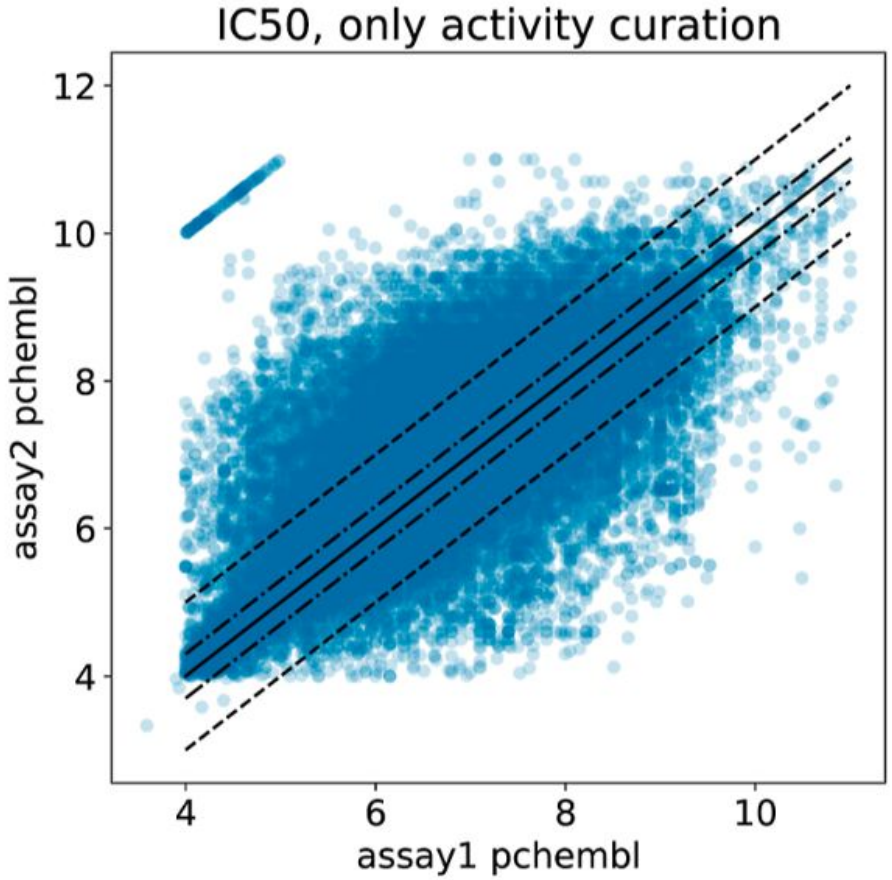
Inspired by Pat's BlogPost
we-need-better-benchmarks-for-machine

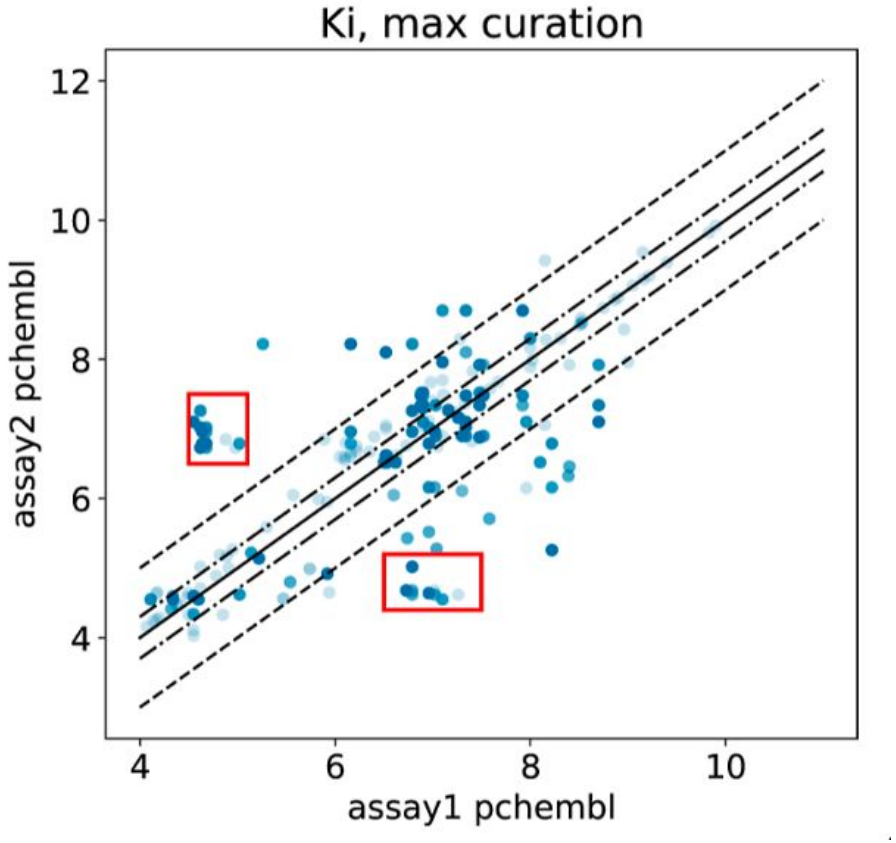
- **Valid structures**
  - Invalid SMILES, not be parsed by standard cheminformatics tools (e.g. rdkit)
- **Consistent chemical representations**
  - Standardized based on accepted conventions
- **Stereochemistry**
  - We need to know the correct structure
- **Consistent measurements**
  - Ideally experiments performed in same lab, but at least same standards
- **Realistic dynamic range and cutoffs**
  - Typical range: solubilities between 1 and 500 µM (cut at both ends '<' an '<')
  - Sensible cut-off choices for classification
- **Clear definitions of training, validation, and test sets**
  - Data leakage: random, scaffold and cluster splits
  - IDs need to be given in benchmark
- **Data curation errors**
  - Duplicate structures with differing labels

***Not so good* examples from MoleculeNet**

- 11 SMILES with uncharged tetravalent nitrogen atom in BBB
- 59 beta-lactam antibiotics in BBB, carboxylic acid in three different forms
- 71% of the molecules in BACE have at least one undefined stereocenter
- BACE data collected from 55 papers
- ESOL spans 13 logs, easy to separate

# Inconsistent Data Can Make ML Modeling Difficult




Landrum, Gregory A., and Sereina Riniker. "Combining IC50 or K i values from different sources is a source of significant noise." *Journal of Chemical Information and Modeling* 64.5 (2024): 1560-1567.

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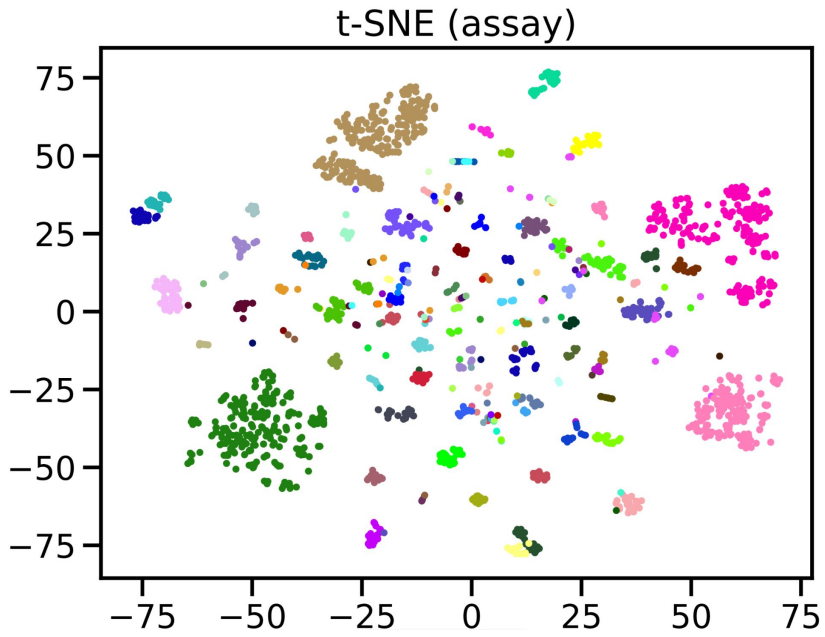
15

# Typical Challenges in (Public) Chemical Datasets

- Different experimental protocols
- Inconsistent values
- Missing documentation
- Data tends to be heavily clustered

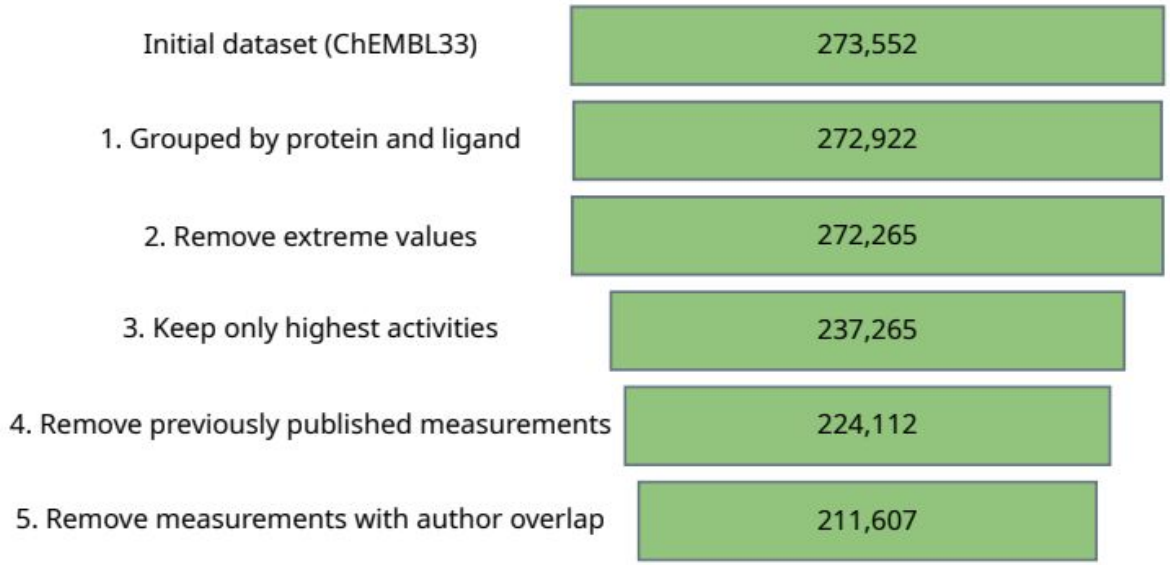



- kinodata-EGFR ligand activities
- t-SNE on 2048 bit Morgan fingerprints
- colors = assays

# How to Preprocess such Data Properly?

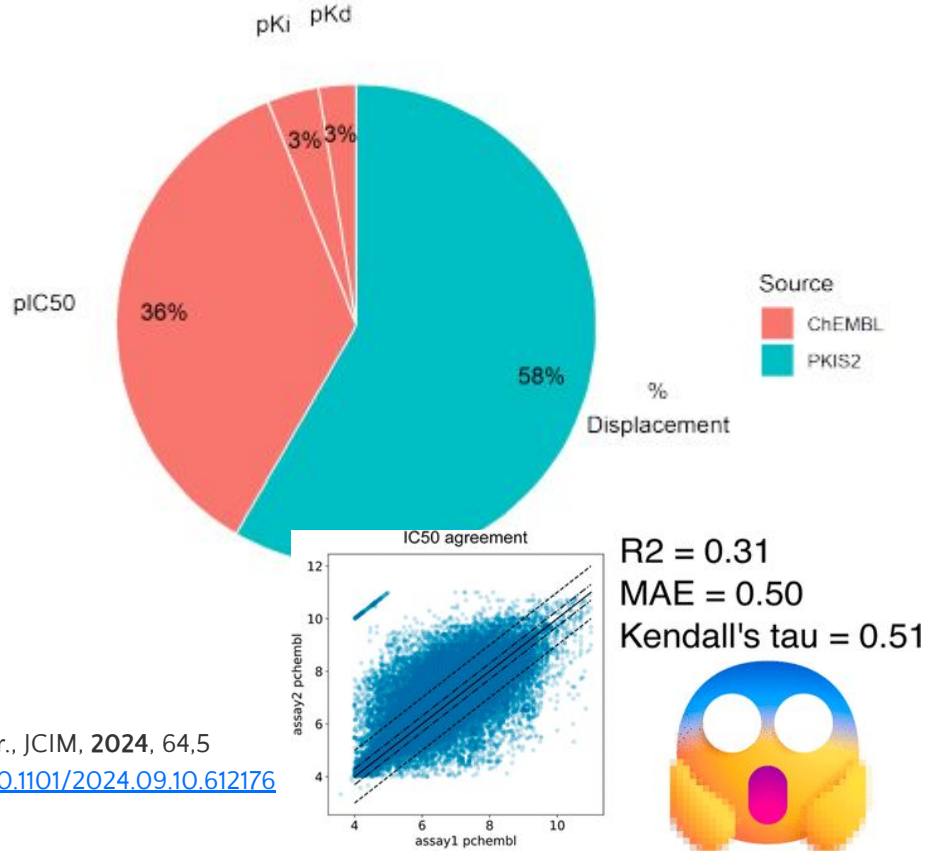
- Automated curation pipeline to reduce errors and to increase reliability

see Kramer, et al. *JMedChem* **2012**; 55(11):5165–5173




López-Ríos de Castro, *et al.*, *biorxiv*, **2024**
https://doi.org/10.1101/2024.09.10.612176

- Bioactivity assay measurement classes vary by and within data set




Landrum, Riniker., JCIM, **2024**, 64,5
https://doi.org/10.1101/2024.09.10.612176

# Applying ML to Drug Design with Trust

**Do I have the right data?**

**Can I trust this prediction?**

**Is the model interpretable?**

(Skipped due to time constraints)

- Model validation and data splits
- Model generalizability and applicability

# Is My Training Data Relevant?

**Machine learning is all about labeling things using examples**

**If I train on this?**

**Can I predict this?**

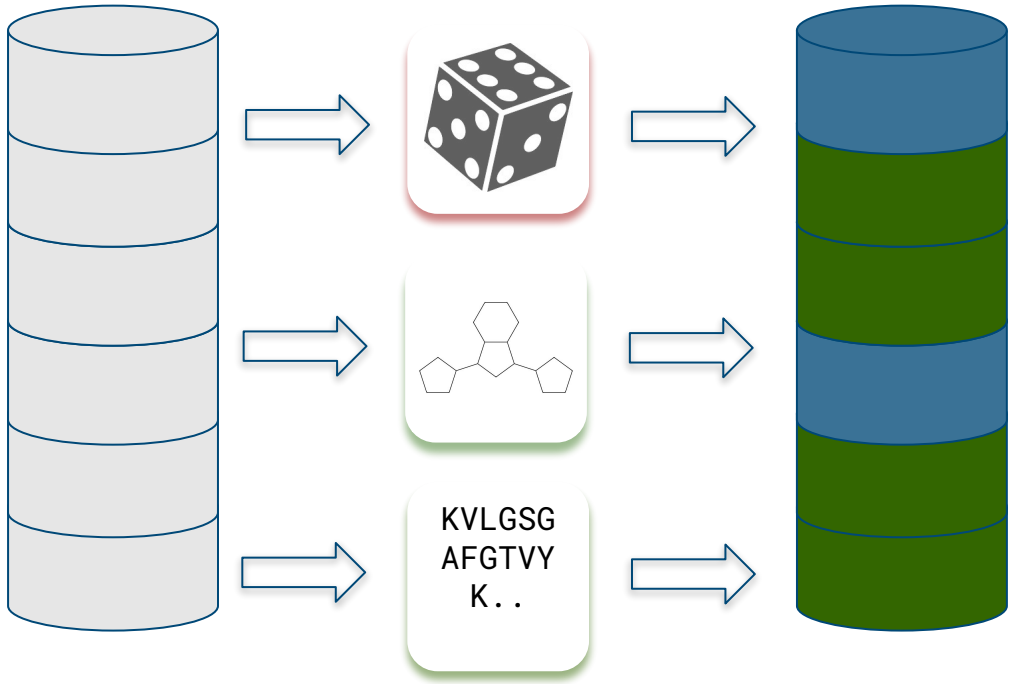
# Example Scenarios

**Can I predict properties for my molecules based on literature data?**

**Can I make predictions for a new project from my existing data?**

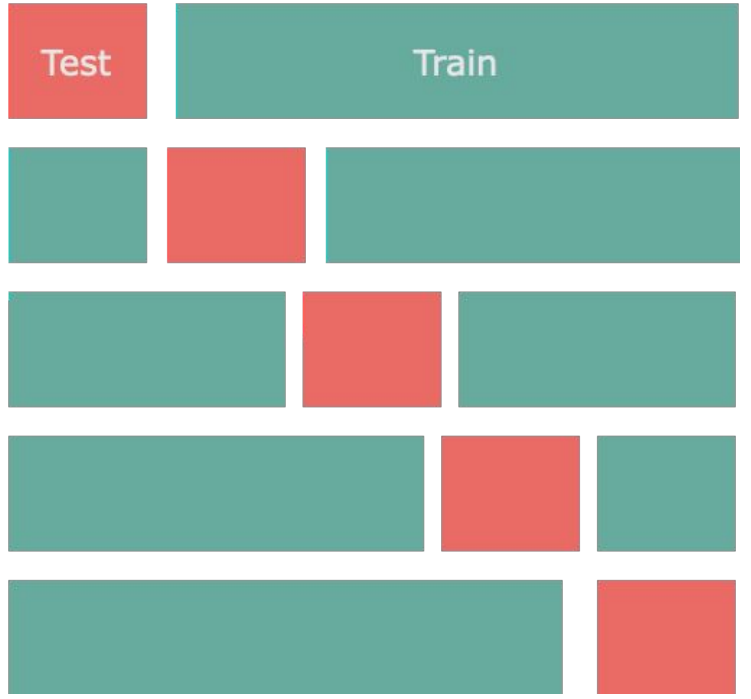
# Data Split is Crucial to Assess Generalizability

- Train/val/test split
- Random splits overestimate out-of-domain generalization
- Better: Splits based on
  - Ligand scaffold
  - Protein sequence

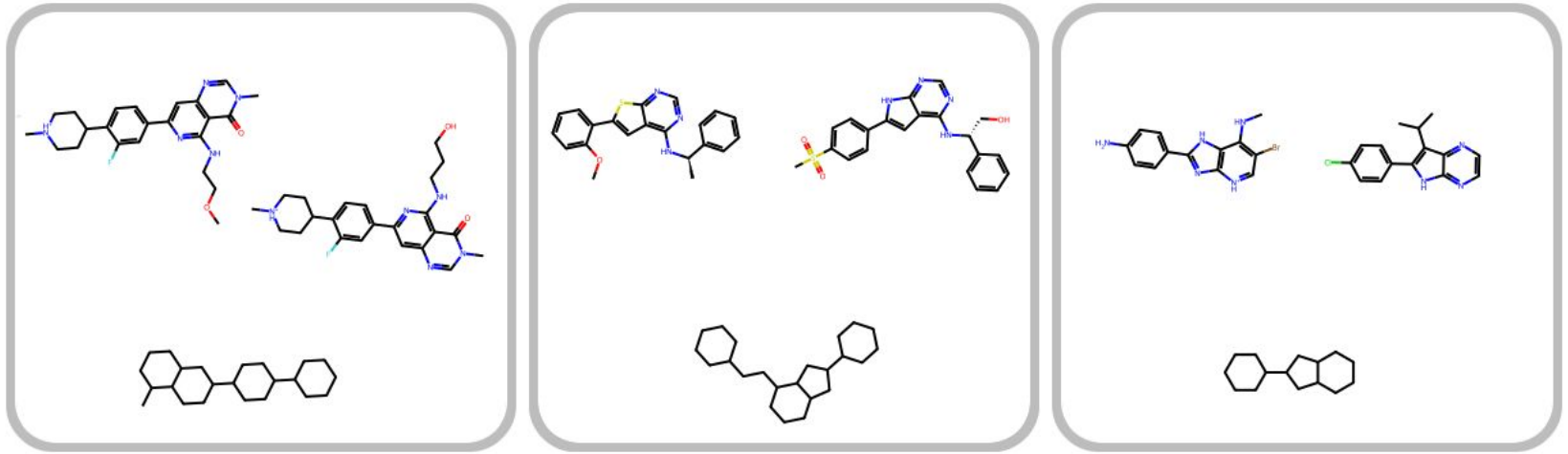


# Grouped k-Fold Split

- Folds are in accordance with groups (scaffold clusters)
- Every data point is part of the test set *exactly once*
- Folds may not be of exact equal size
- Consider labels (stratified split)



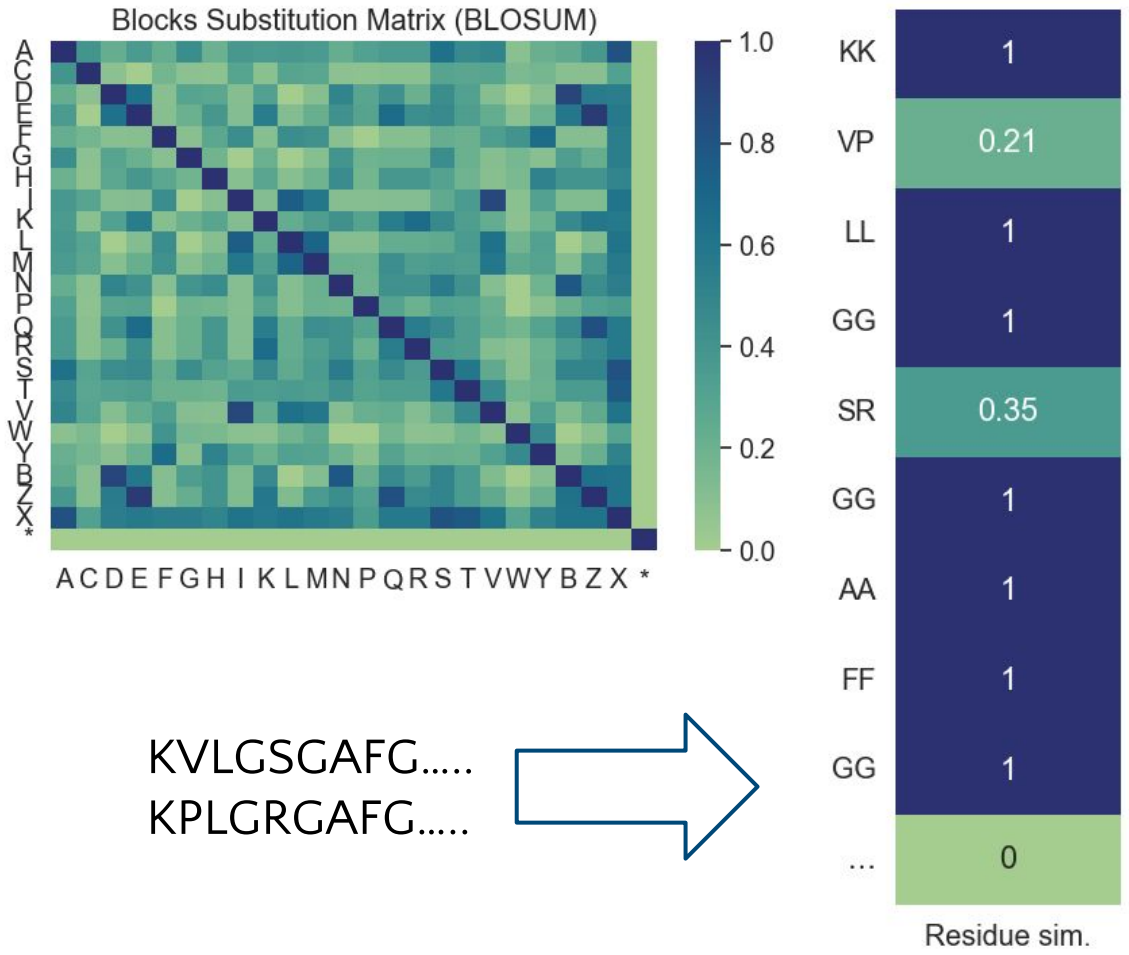
# Data Splits – Scaffold Split



- Avoid data leakage over structurally similar ligands
- Group by generic scaffold *(or similarity)*
- Ensure each group only in one of {train, test, val}

# Data Splits – Target-Based Split

- Cluster pocket sequences based on BLOSUM-similarity
- Generate splits by randomly assigning clusters to {train, val, test}



# DataSAIL – Data Splitting Against Information Leakage

**Developed by Roman Joeres at Prof. Kalinina's lab, Saarland University**
**uses mathematical optimization to identify the most difficult split**
**https://github.com/kalininalab/DataSAIL**

# Applicability and Uncertainty of Machine Learning Models



Do I have the right data?

Can I trust this prediction?



Is the model interpretable?

**Conformal Prediction**

**Bootstrap**

**Gaussian Process Regression**

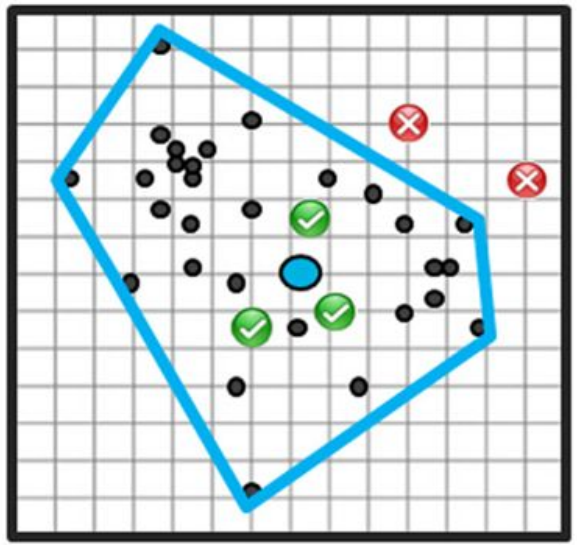
**Jackknife**

**Monte Carlo Dropout**

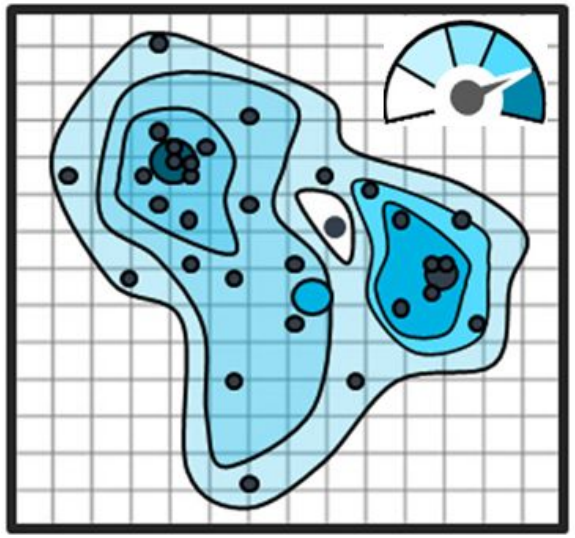
# Applicability Domain

**Definition:** The applicability domain of a (Q)SAR/ML model is the response and chemical structure space in which the model makes predictions with a given reliability.

1. Applicability:
Interpolation within the chemical structure space



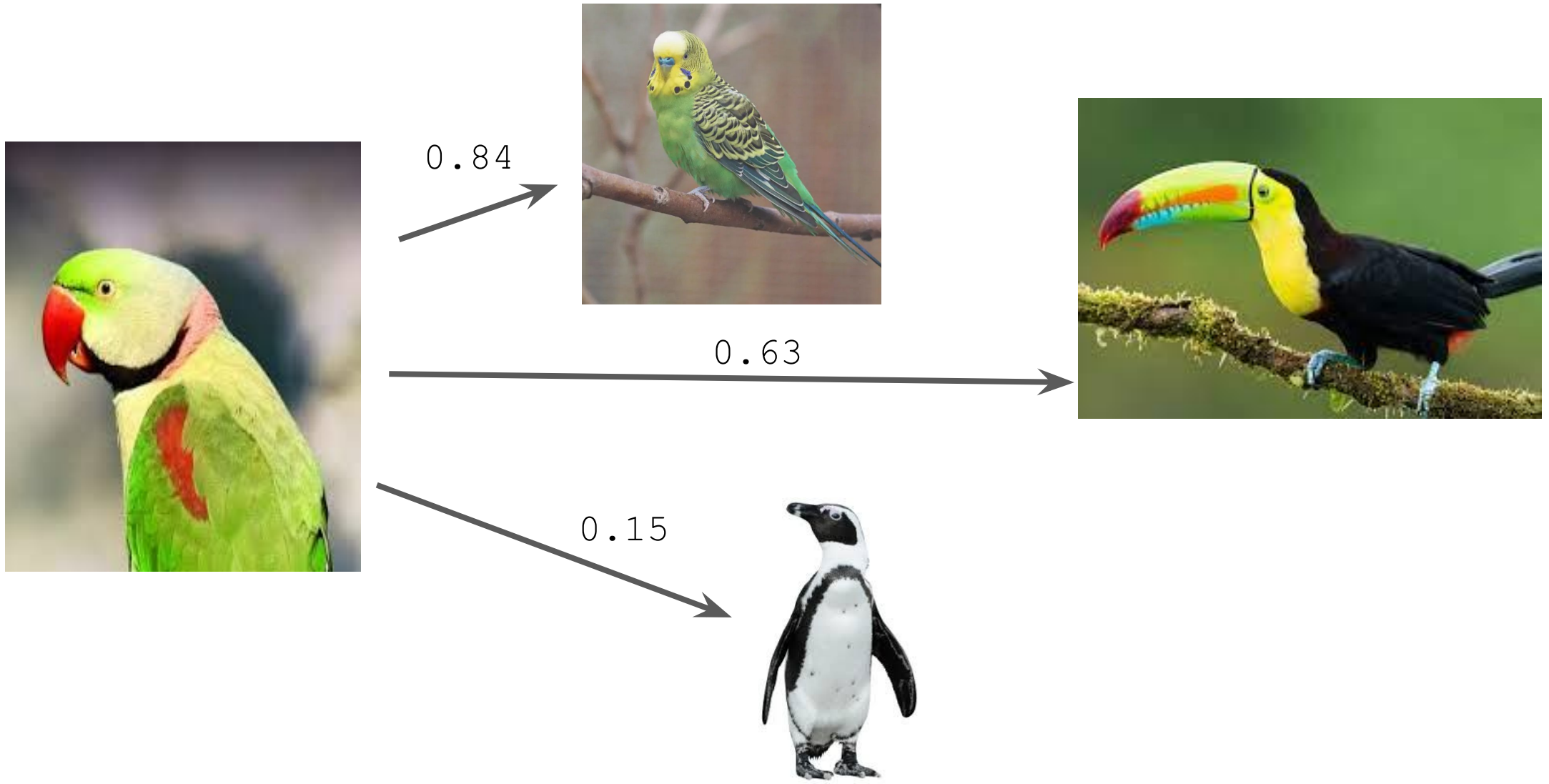
2. Reliability:
Density of knowledge around the query chemical structure



3. Decidability:
Distance of the query chemical compound to the decision boundary of model

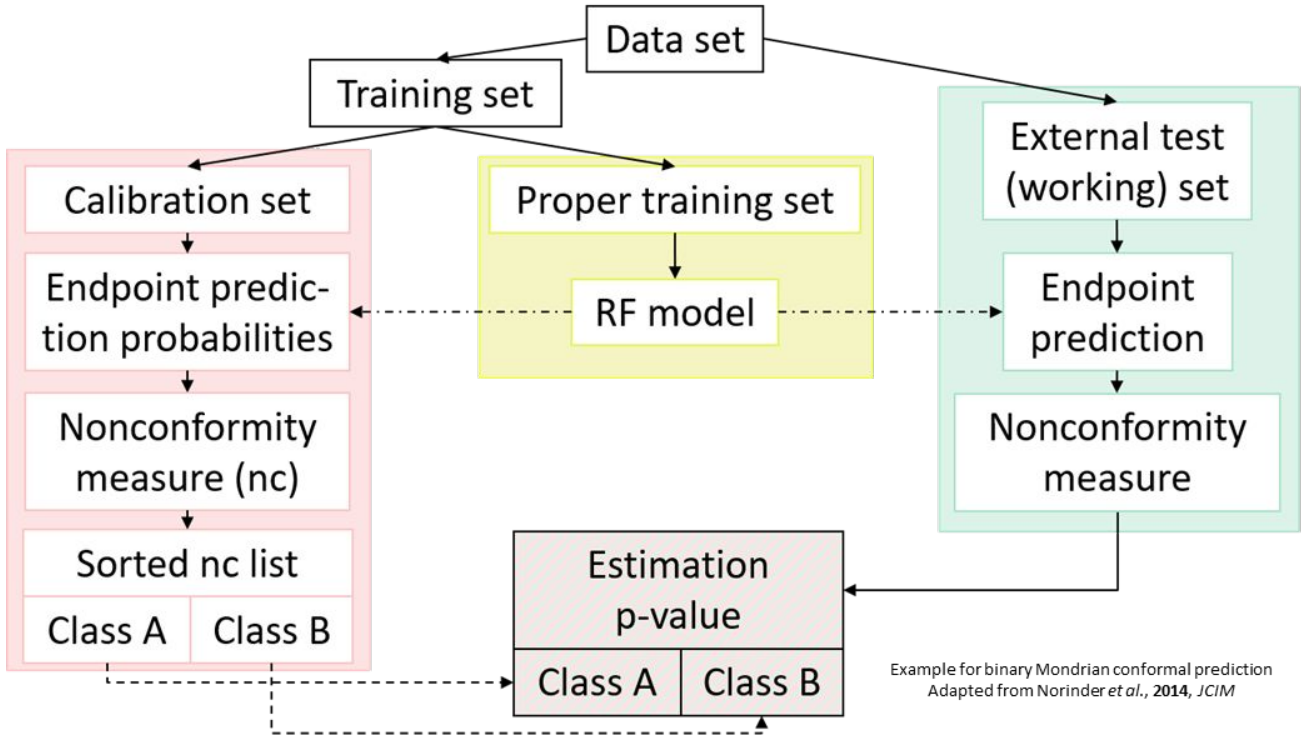
Figures taken from: Hanser, *et al.*, *SAR and QSAR in Environmental research*, **2016**, 27:11, 865-881

# Using Similarity to Assess Applicability

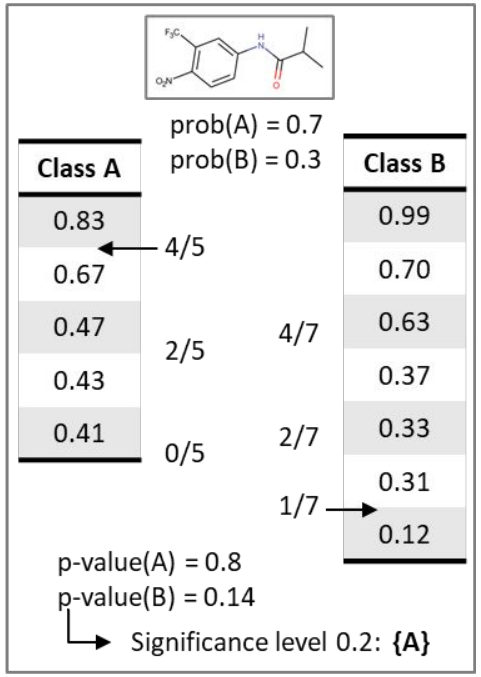


# Conformal Prediction Framework Based on ML

- Statistically valid on a given confidence level (if exchangeability is given)
- Additional calibration step: Compare predictions to those previously seen (p-value)
- Output prediction sets in binary classification: **{A}, {B}, {A,B}** or **{ }**
- Validity = % of correct classifications
- Efficiency = % of single class predictions




Example for binary Mondrian conformal prediction
Adapted from Norinder *et al.*, **2014**, *JCIM*



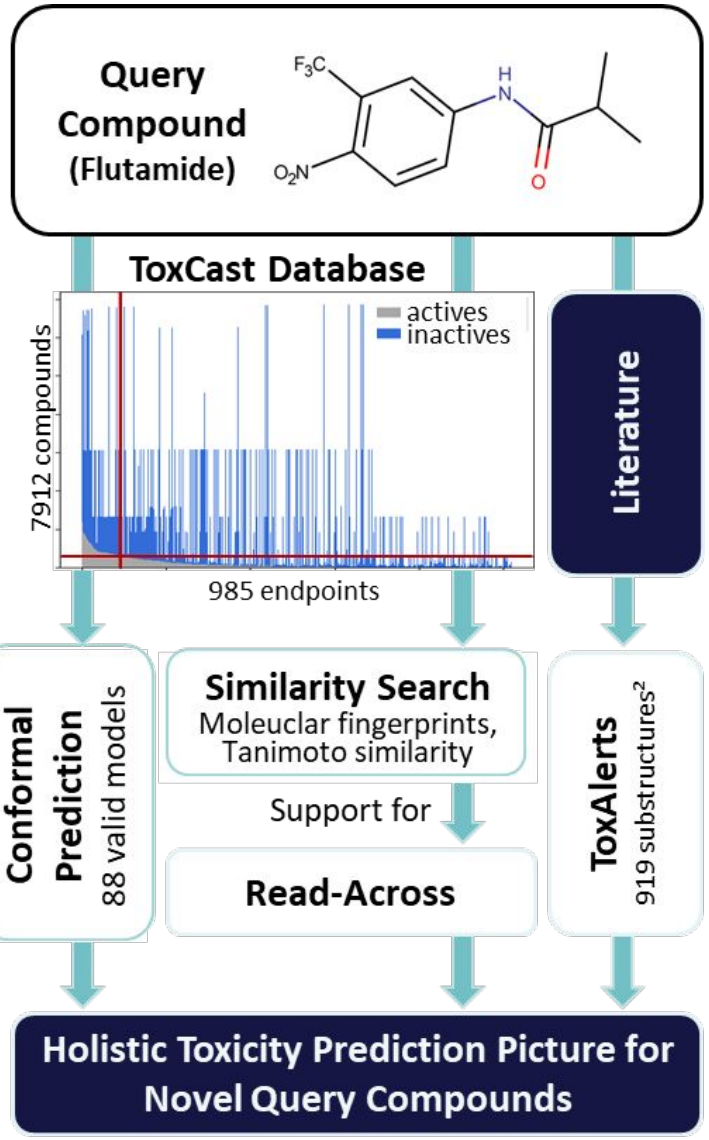
# Know-Tox – Predictions with Confidence

- ToxCast data set
  - ~ 8000 compounds * 1000 endpoints (sparse)
  - Pharmaceutical, pesticides, environmental chemicals
  - Cell cycle, steroid receptors, cytotoxicity, …

Can we apply the model to new (BASF) data?

- Conformal prediction
  - Case study: Antiandrogen activity (AA)
  - Validity, efficiency and accuracy like other studies

| | Dataset | Efficiency | Accuracy (SCPs) all | cl.1 | cl.0 | # toxic/ non-toxic |
|---|---|---|---|---|---|---|
| cross-validation | ToxCast AA | 0.87 | 0.78 | 0.80 | 0.78 | 868/5842 |
| external | Norinder[3] | 0.79 | 0.68 | 0.70 | 0.67 | 160/201 |
| In-house | BASF (I) | 0.94 | **0.56** | **0.97** | **0.07** | 280/254 |




https://github.com/volkamerlab/knowtox_manuscript_SI

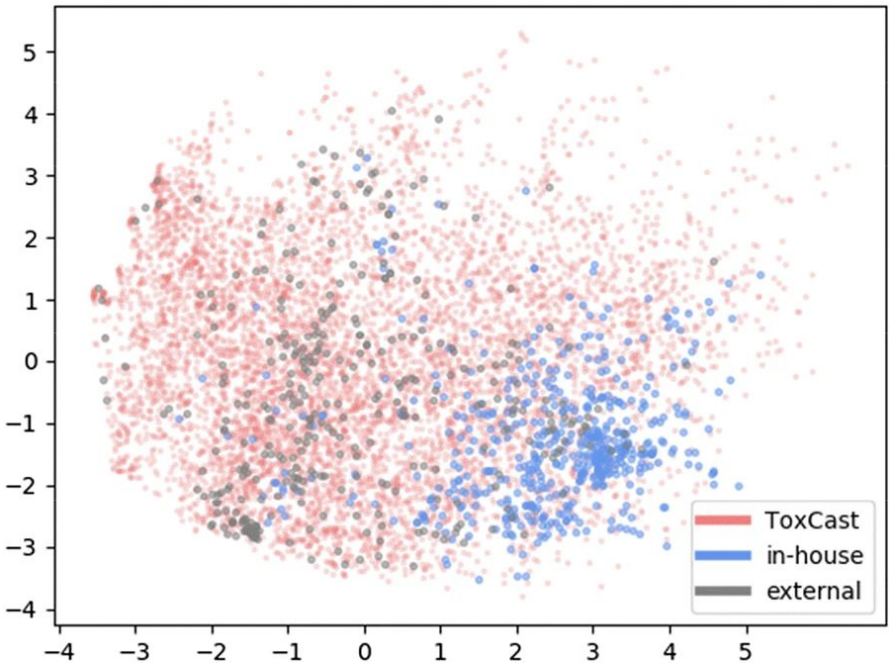
# Know-Tox – Predictions with Confidence

- ToxCast data set
  - ~ 8000 compounds * 1000 endpoints (sparse)
  - Pharmaceutical, pesticides, environmental chemicals
  - Cell cycle, steroid receptors, cytotoxicity, …

Can we apply the model to new (BASF) data?

- Conformal prediction
  - Case study: Antiandrogen activity (AA)
  - Validity, efficiency and accuracy like other studies
  - kNN normalization & balancing
  - Less efficient, but higher accuracy

| | Dataset | Efficiency | Accuracy (SCPs) all | cl.1 | cl.0 | # toxic/ non-toxic |
|---|---|---|---|---|---|---|
| cross-validation | ToxCast AA | 0.87 | 0.78 | 0.80 | 0.78 | 868/5842 |
| external | Norinder[3] | 0.79 | 0.68 | 0.70 | 0.67 | 160/201 |
| In-house | BASF (I) | 0.94 | **0.56** | **0.97** | **0.07** | 280/254 |
| | BASF (II) | **0.20** | **0.75** | **0.80** | **0.71** | 280/254 |

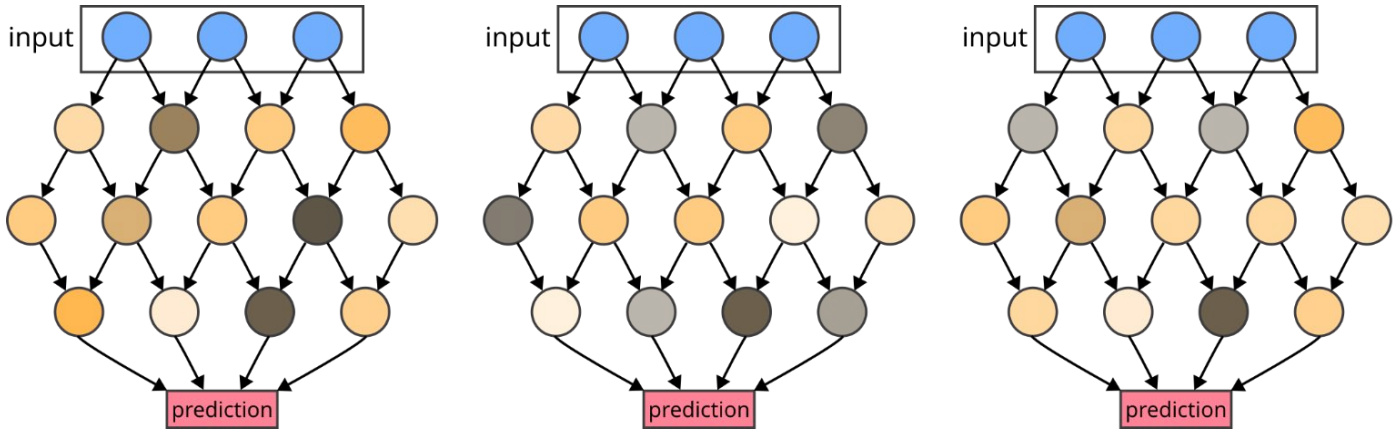



Descriptor space of a 2-component PCA trained on ToxCast-AA data

Morger, A., *et al. J Cheminform* 12, 24 (**2020**)
https://github.com/volkamerlab/knowtox_manuscript_SI

# Using Uncertainty to Assess Model Confidence

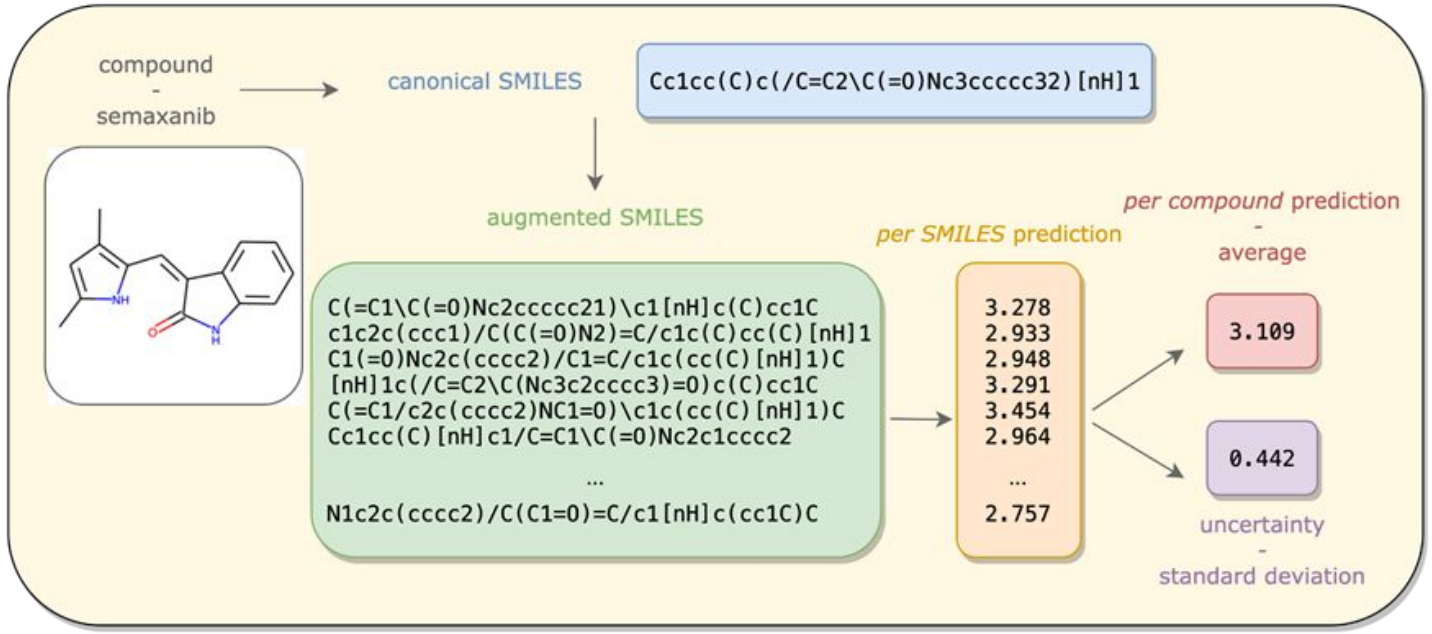
- **Single deterministic methods**
  - Classification setting: predicted class probabilities
  - Secondary model trained to predict uncertainty for an already trained model
- **Ensemble methods**
  - Ensemble of similar but different models -> Variance as uncertainty
  - Varying random seeds, resulting in different weights
  - Varying the training data (*bagging*)
- **Training- and test-time data augmentation**
  - Augmeted set of points using stochastic noise or domain knowledge

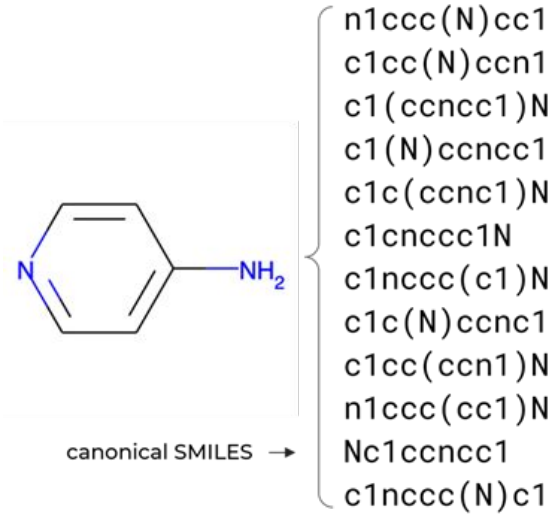



https://github.com/volkamerlab/teachopencadd

# SMILES Augmentation Improves Model Performance

Maximizing molecular property prediction performance with confidence estimation using SMILES augmentation and DL




Kimber *et al., AI in Life Sciences,* **2021**, 1, 100014
https://github.com/volkamerlab/maxsmi

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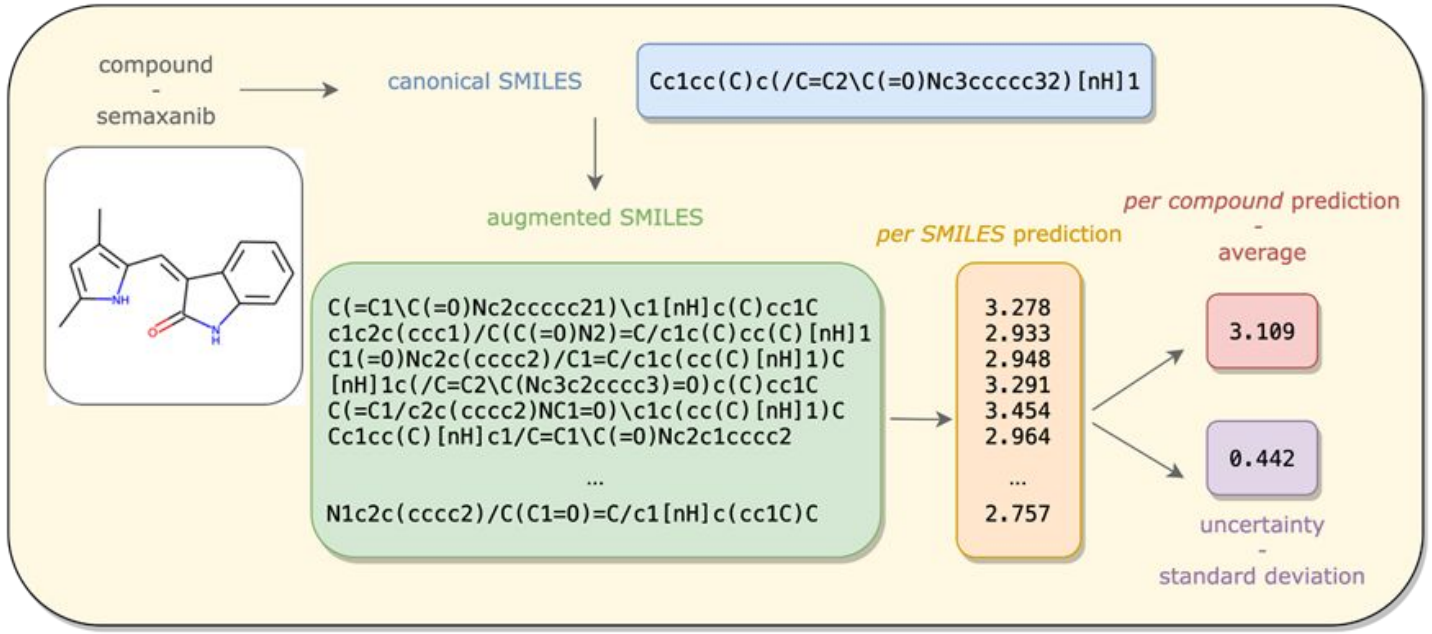
# SMILES Augmentation Improves Model Performance

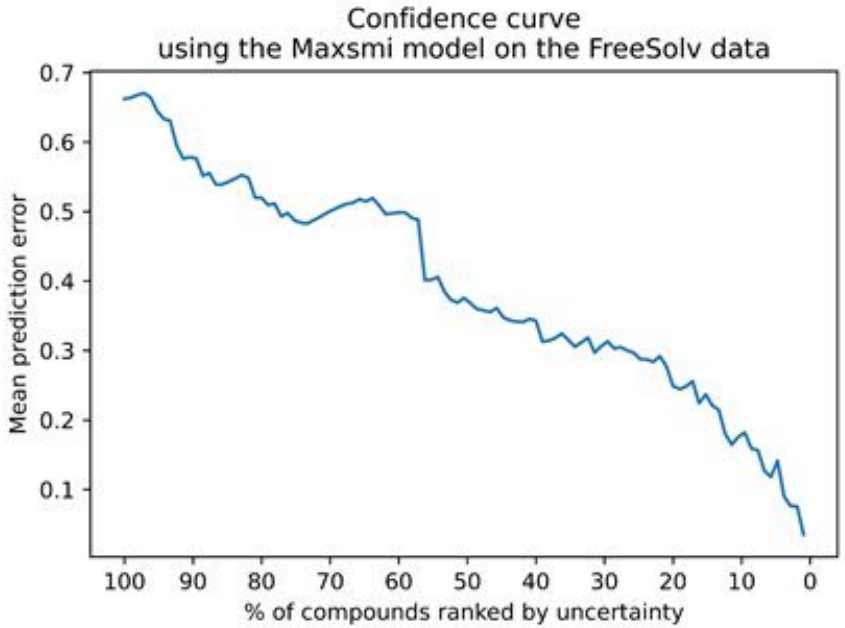
Maximizing molecular property prediction performance with confidence estimation using SMILES augmentation and DL




Kimber *et al., AI in Life Sciences,* **2021**, 1, 100014
https://github.com/volkamerlab/maxsmi

**Uncertainty prediction**

More confident model implies smaller prediction error

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# TeachOpenCADD in a Nutshell

https://github.com/volkamerlab/teachopencadd

**What?** Pipelines for common CADD* tasks using open resources

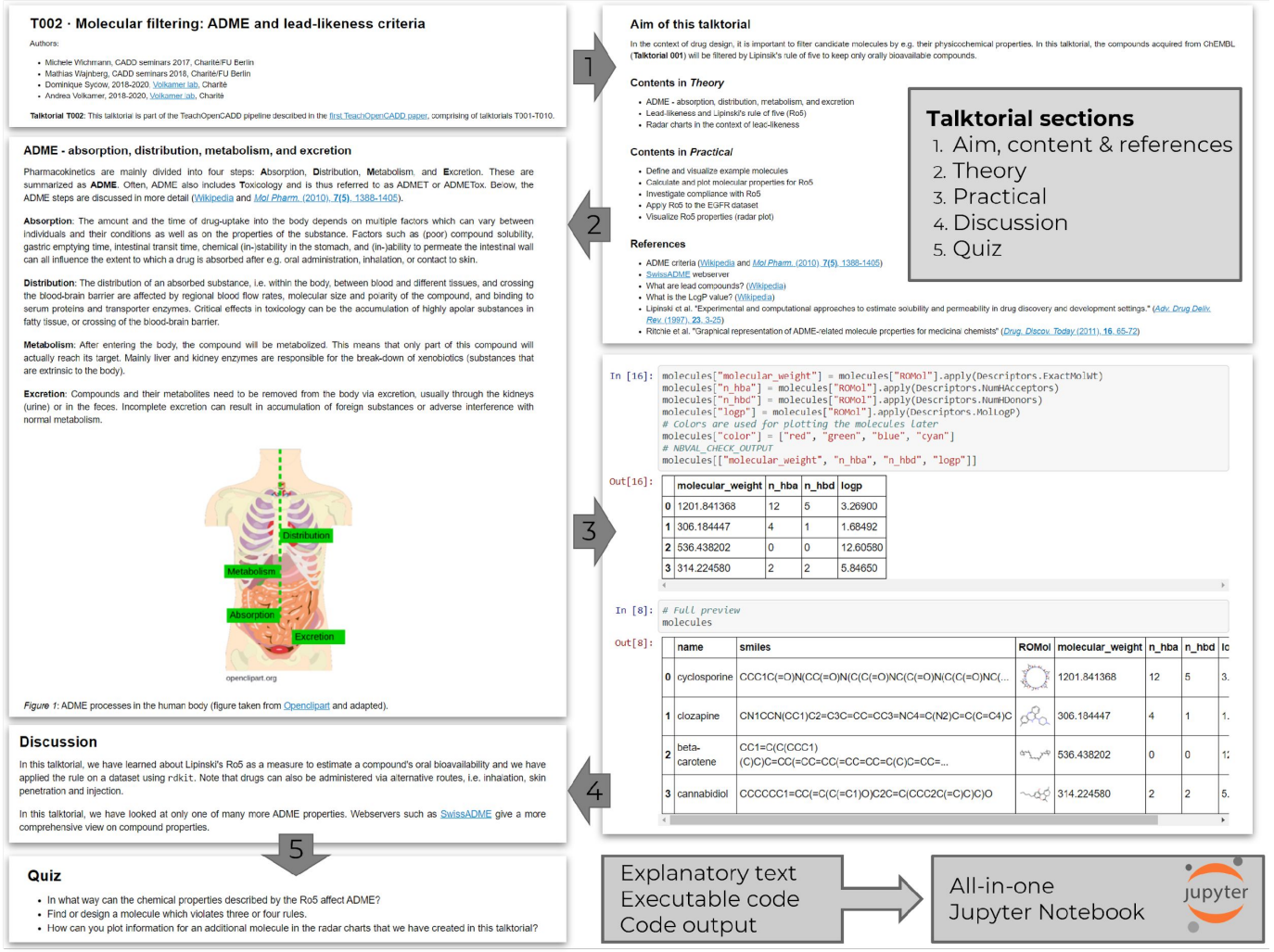
**How?** Coding-based Jupyter notebooks[1] (Python) & GUI-based KNIME workflows[2]

jupyter  Open for Innovation KNIME

**For what?** Teaching, self studies & starting point for research projects

**From and for whom?** Students, group, community -> Beginners & advanced users

*CADD = computer-aided drug design

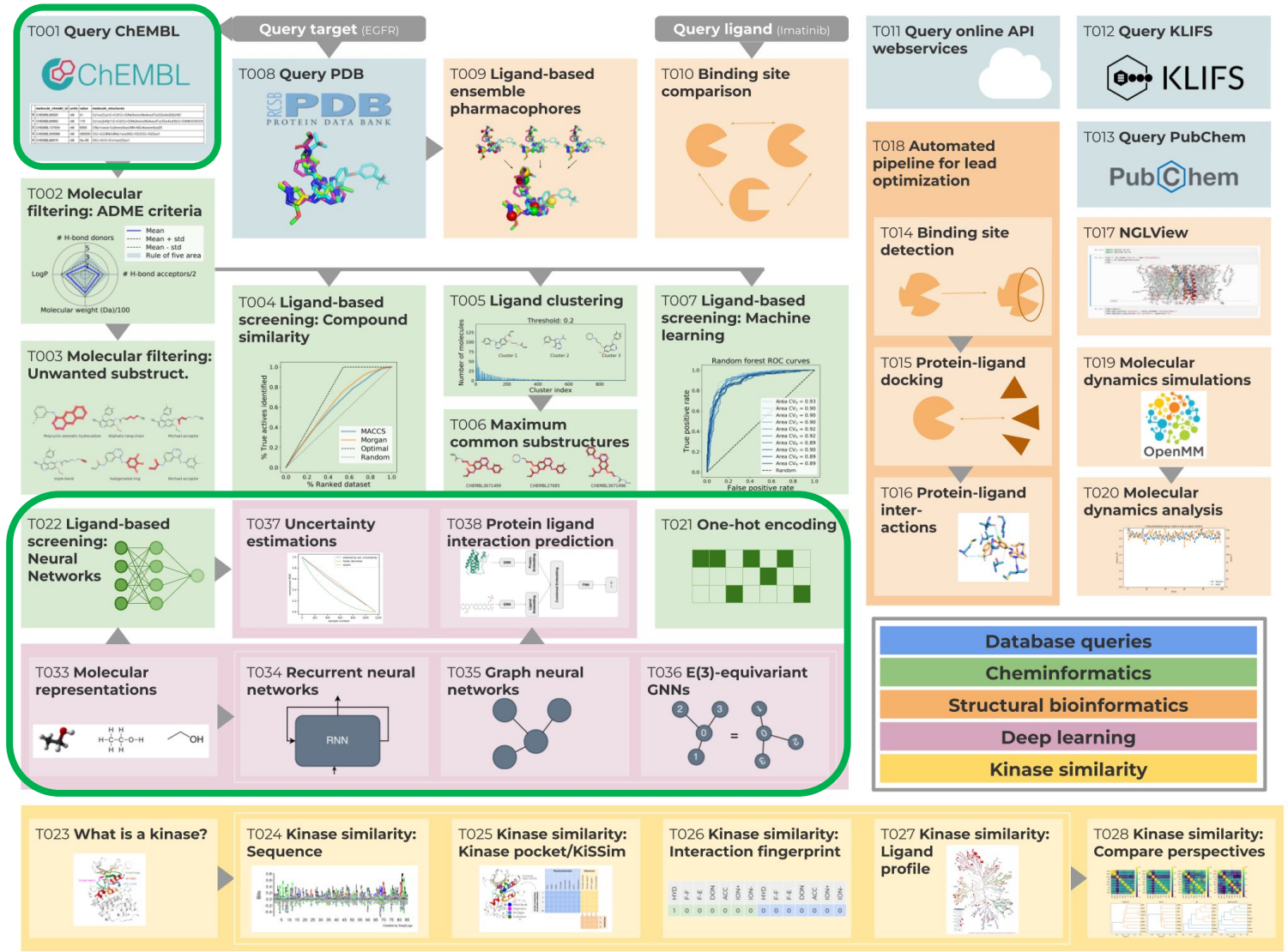


# TeachOpenCADD – Open-Source Python Pipelines

**Relevant for today's session:**

**API queries**

**DL examples**




**Kinase-centric structure-based ML**
https://github.com/openkinome

Lessons learned during the journey of data: from experiment to model for predicting kinase affinity, selectivity, polypharmacology, and resistance, López-Ríos de Castro, *et al.*, *biorxiv*, **2024**
https://doi.org/10.1101/2024.09.10.612176

https://github.com/volkamerlab/teachopencadd

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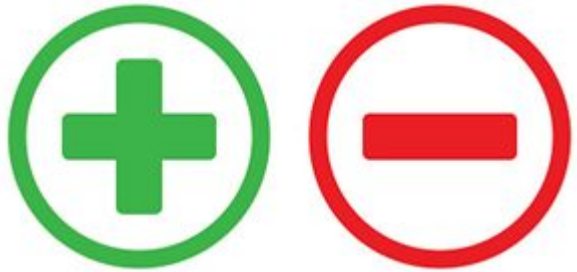
# Take Home Messages

- More data available
- Increased computational power
- Advances in neural network algorithms
- Open-source libraries



- True predictive power
- Applicability and reliability
- Interpretability

- **Data quality, relevance and proper processing are key**
- **Proper model evaluation, always consider baselines when applying ML/DL**
- **Check applicability of your model, ideally prospective studies**
- **Open source and reproducibility**

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# Thank you for your attention!