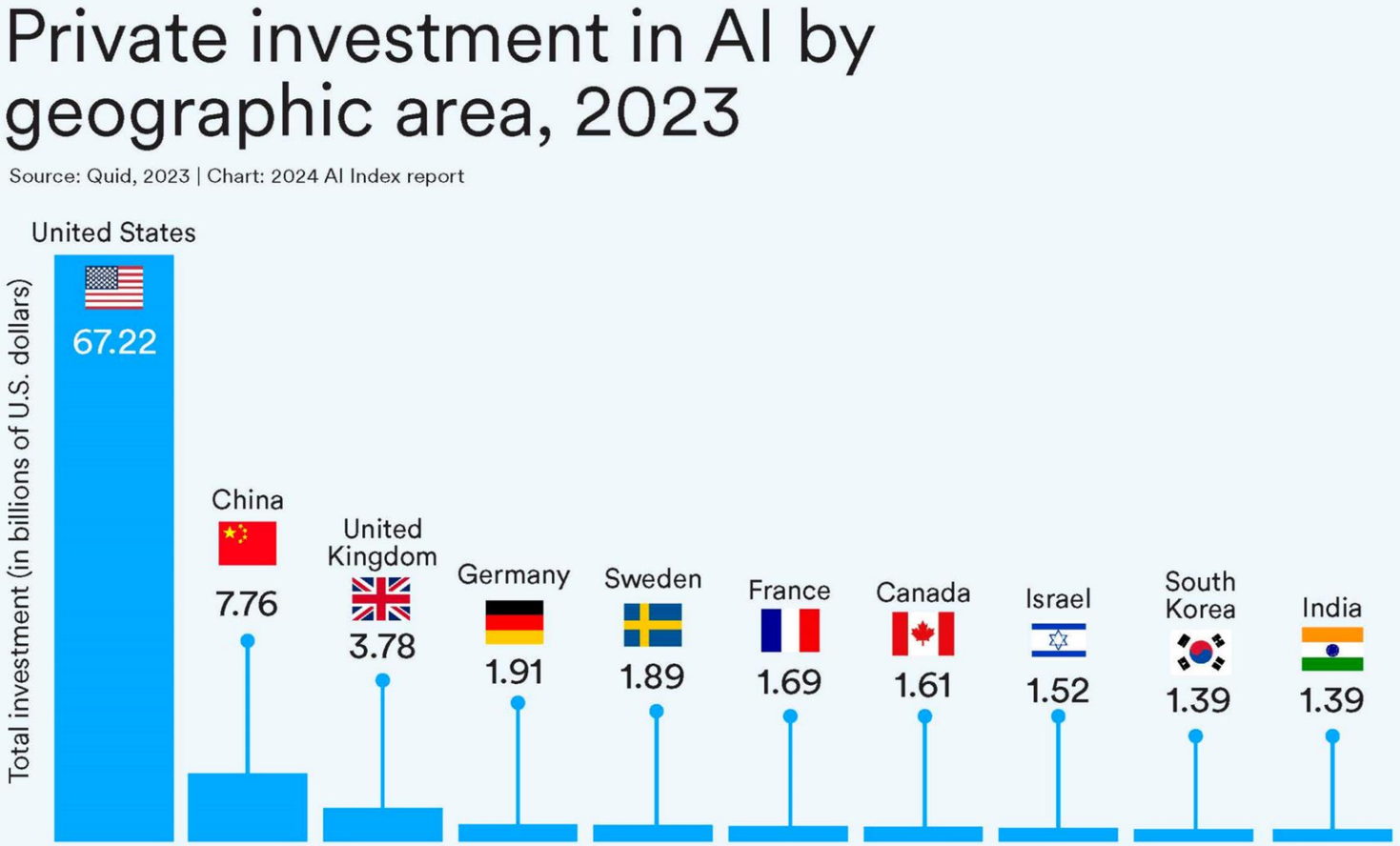
ML to predict chemical outcomes

David Dalmau Ginesta

29/05/2025

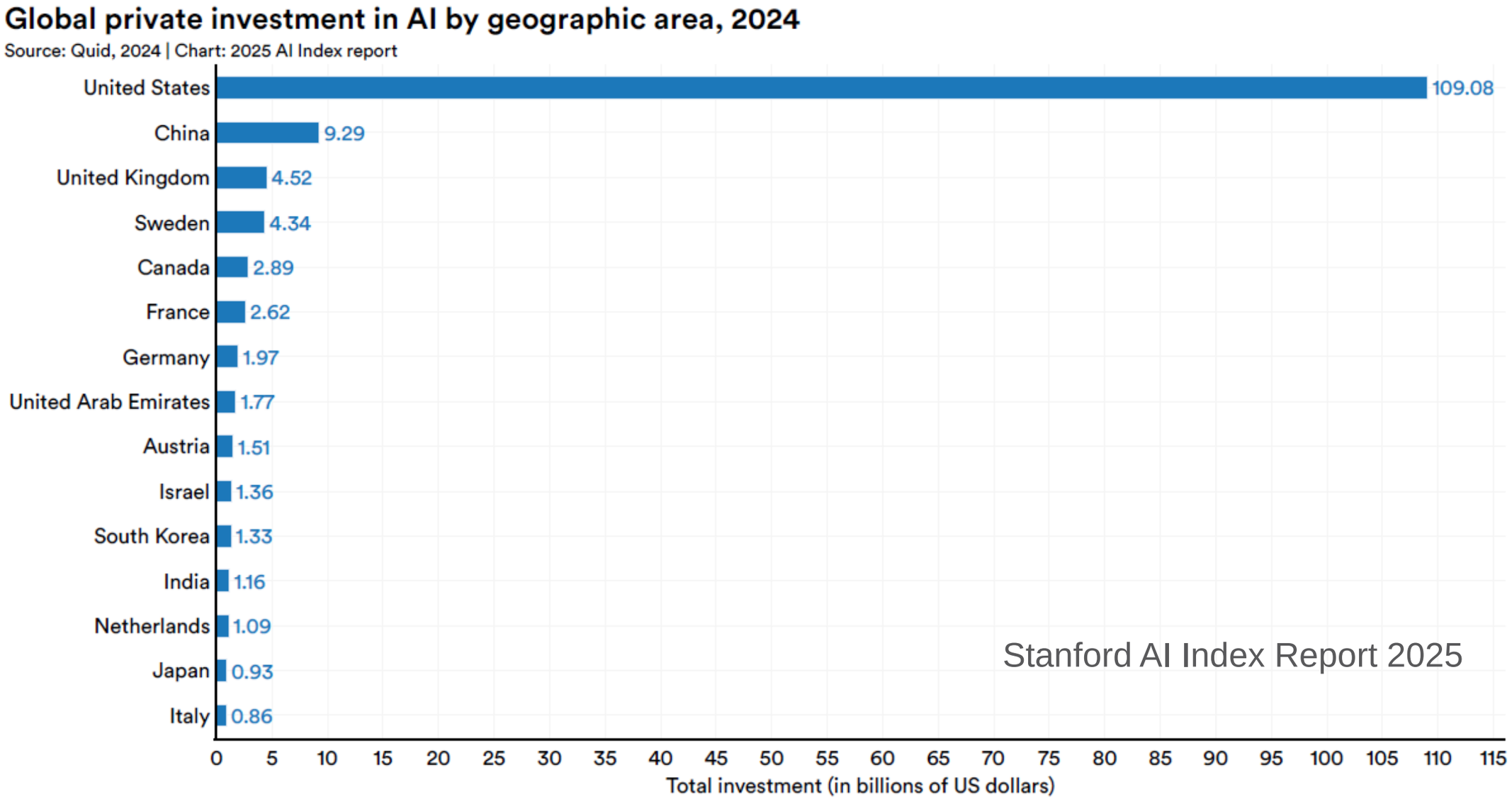
IQCC

Introduction



Stanford AI Index Report 2024

Introduction



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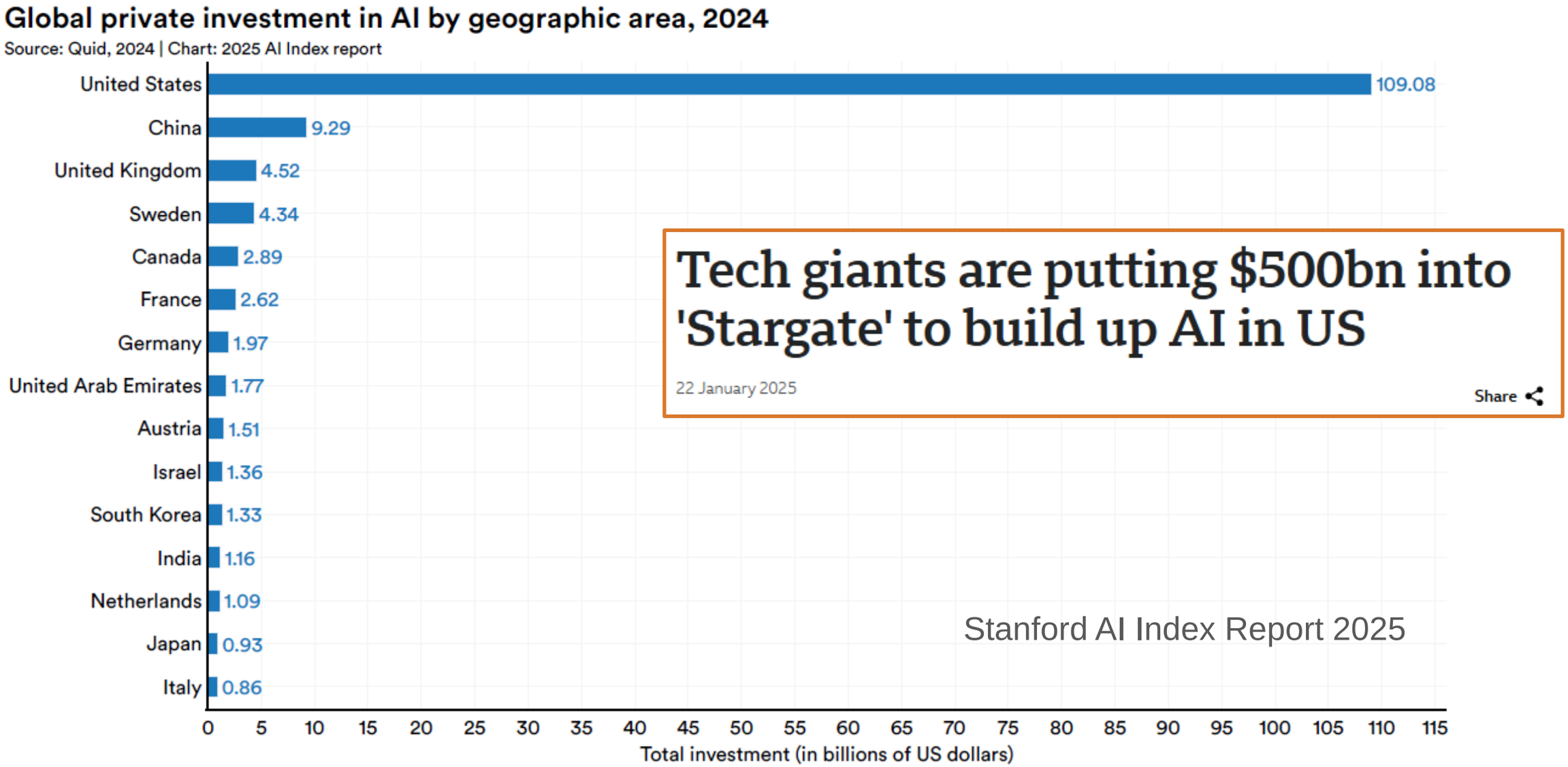

Tech giants are putting $500bn into 'Stargate' to build up AI in US

22 January 2025

Share

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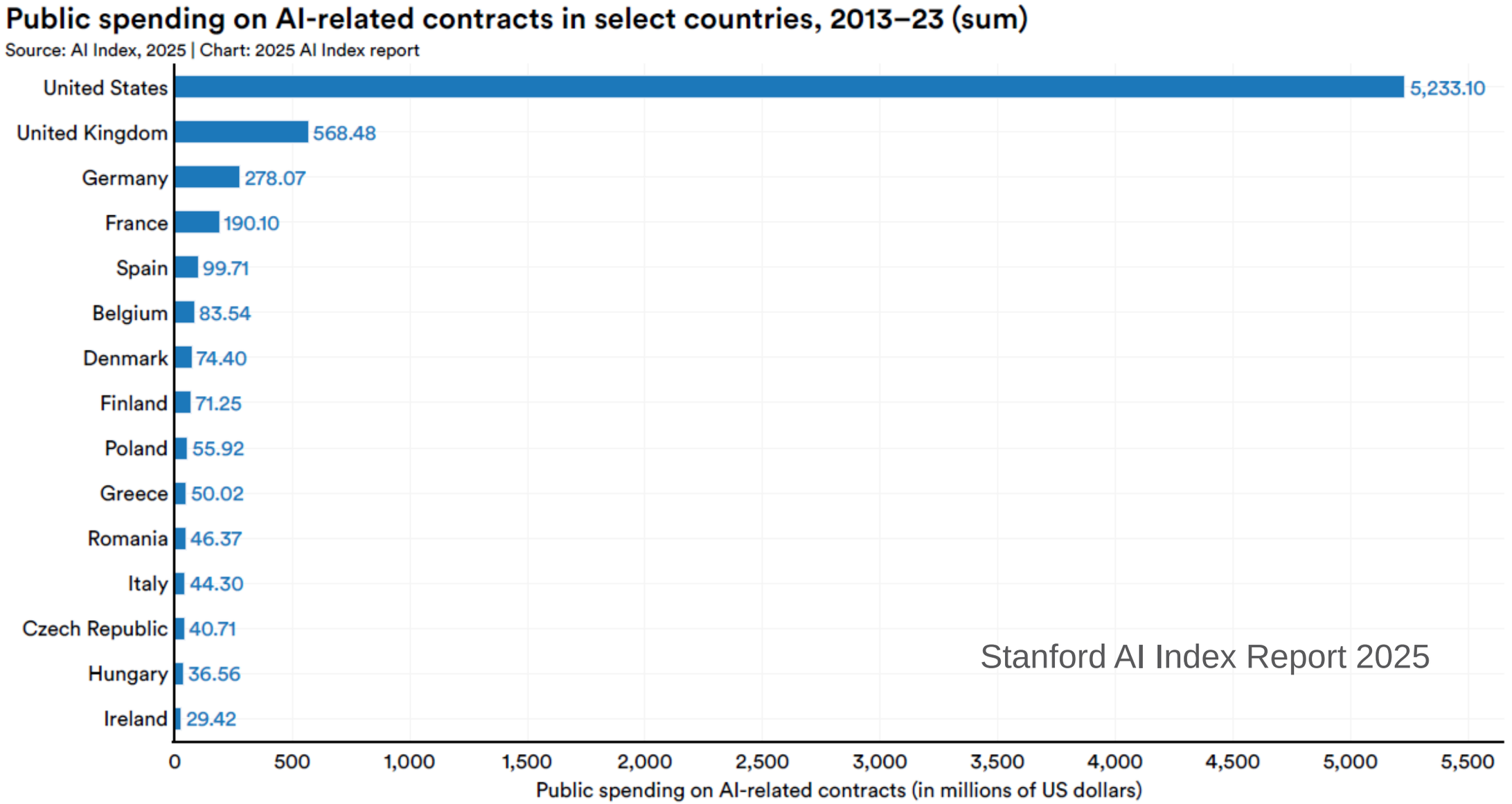

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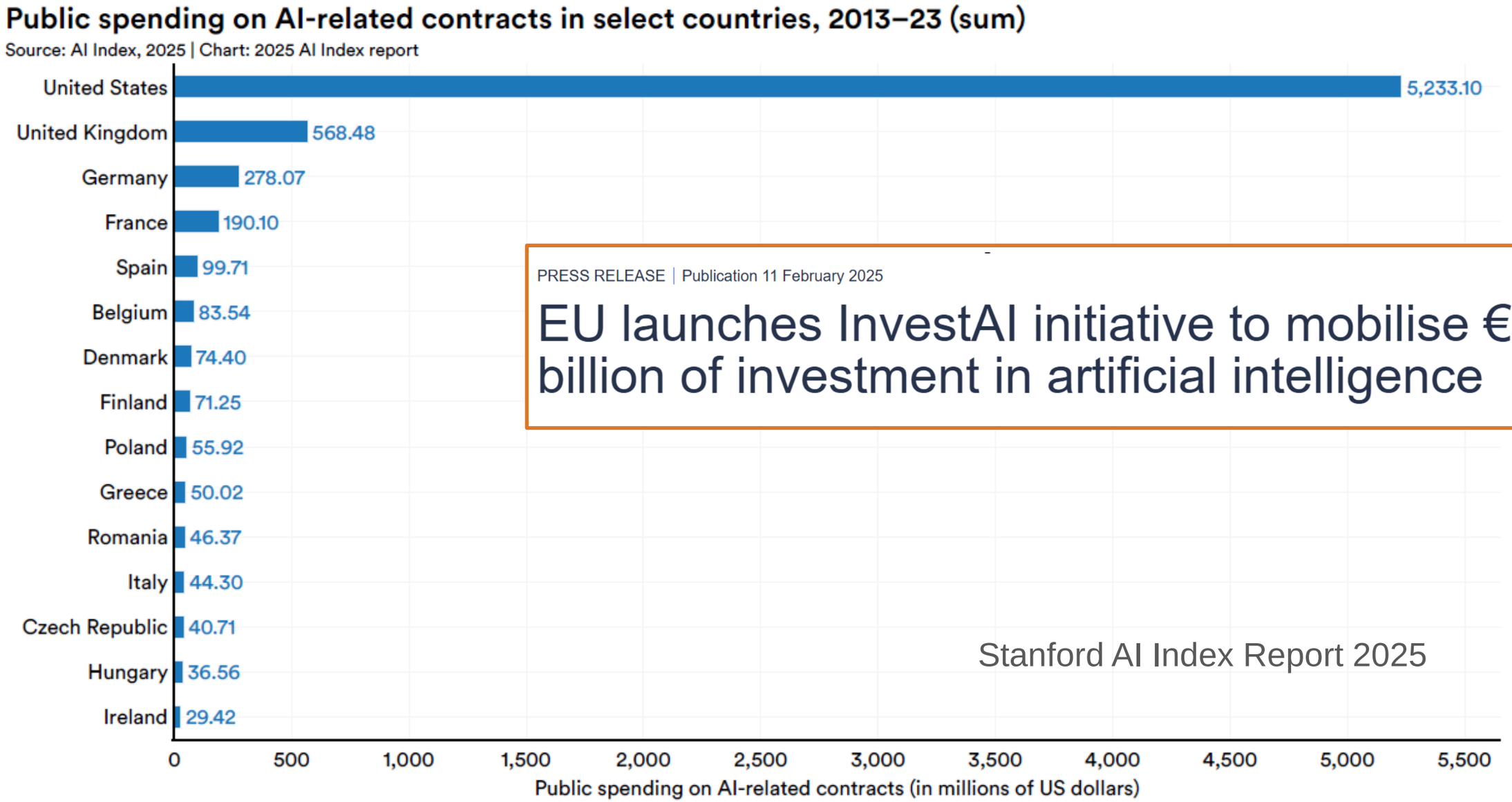
Introduction



PRESS RELEASE | Publication 11 February 2025

EU launches InvestAI initiative to mobilise €200 billion of investment in artificial intelligence

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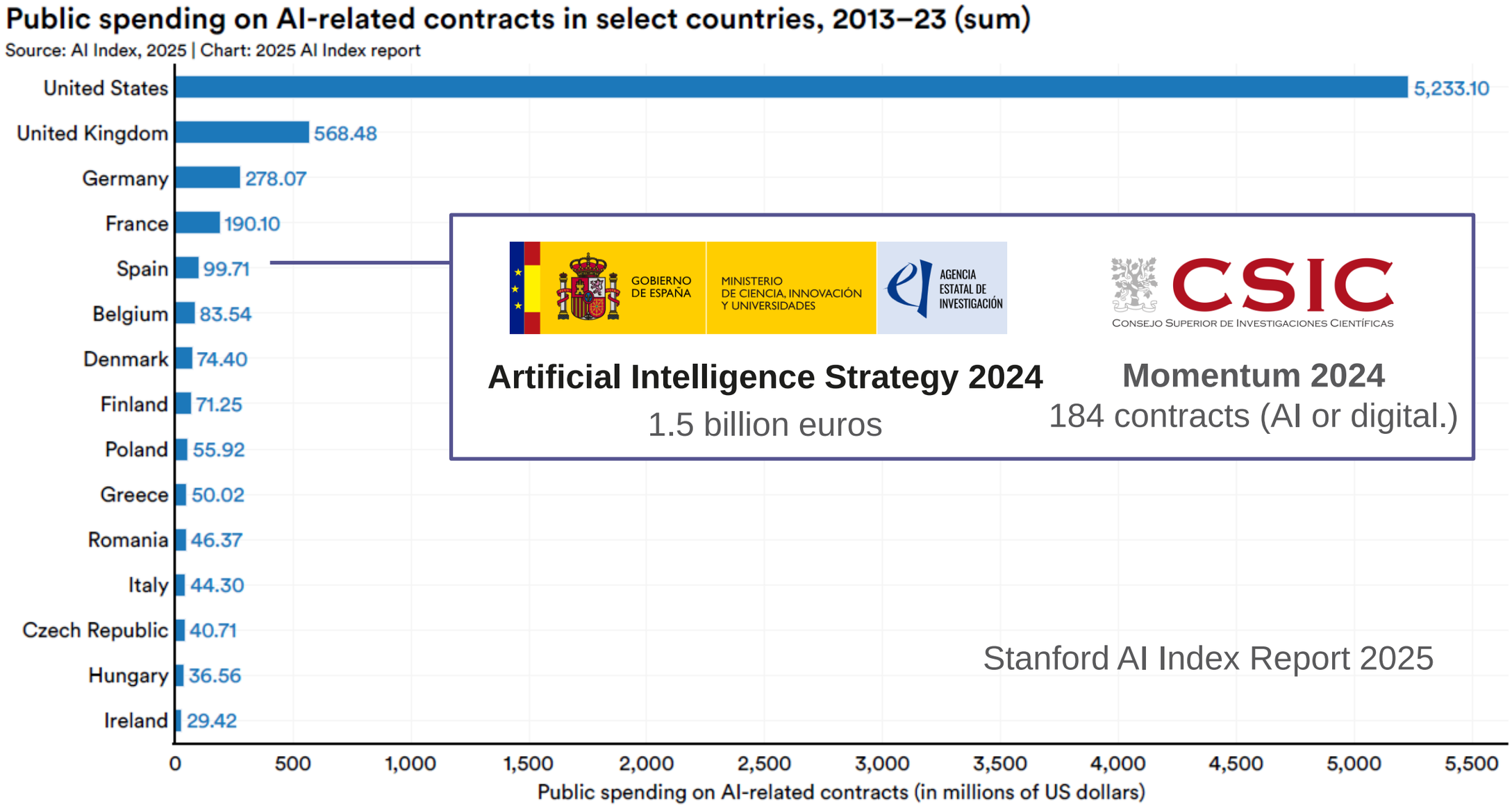
Introduction



GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN

Artificial Intelligence Strategy 2024

1.5 billion euros

CSIC
Consejo Superior de Investigaciones Científicas

Momentum 2024

184 contracts (AI or digital.)

Stanford AI Index Report 2025

Introduction

How does machine learning work?

Data in

ChatGPT

“En un lugar de la Mancha, de cuyo nombre no quiero acordarme, no ha mucho tiempo que vivía un hidalgo de los de lanza en astillero, adarga antigua, rocín flaco y galgo corredor.”

“¡Ser o no ser, esa es la cuestión! - ¿Que debe más dignamente optar el alma noble entre sufrir la fortuna impía el porfiador rigor, o rebelarse contra un mar de desdichas, y afrontándolo desaparecer con ellas?”

ChatGPT, personal communication, February 11, 2023

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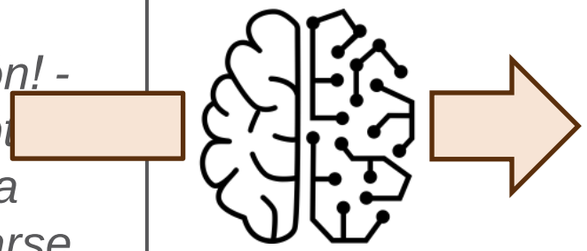

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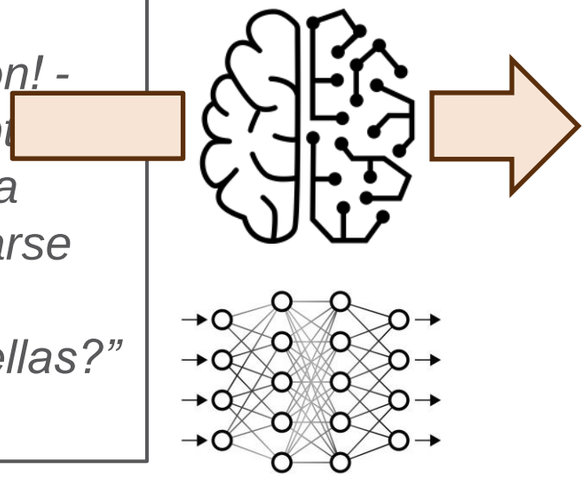

Neural Network

ChatGPT, personal communication, February 11, 2023

Introduction

How does machine learning work?

Data in

Data out

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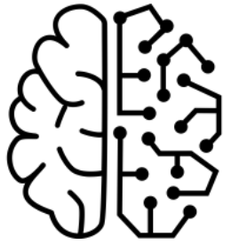
Where does Don Quixote begin?



Who wrote Hamlet?

ChatGPT, personal communication, February 11, 2023

Introduction

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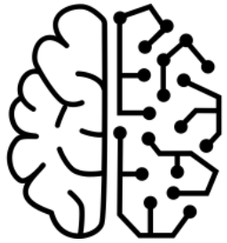

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ChatGPT, personal communication, February 11, 2023

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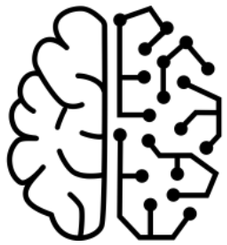

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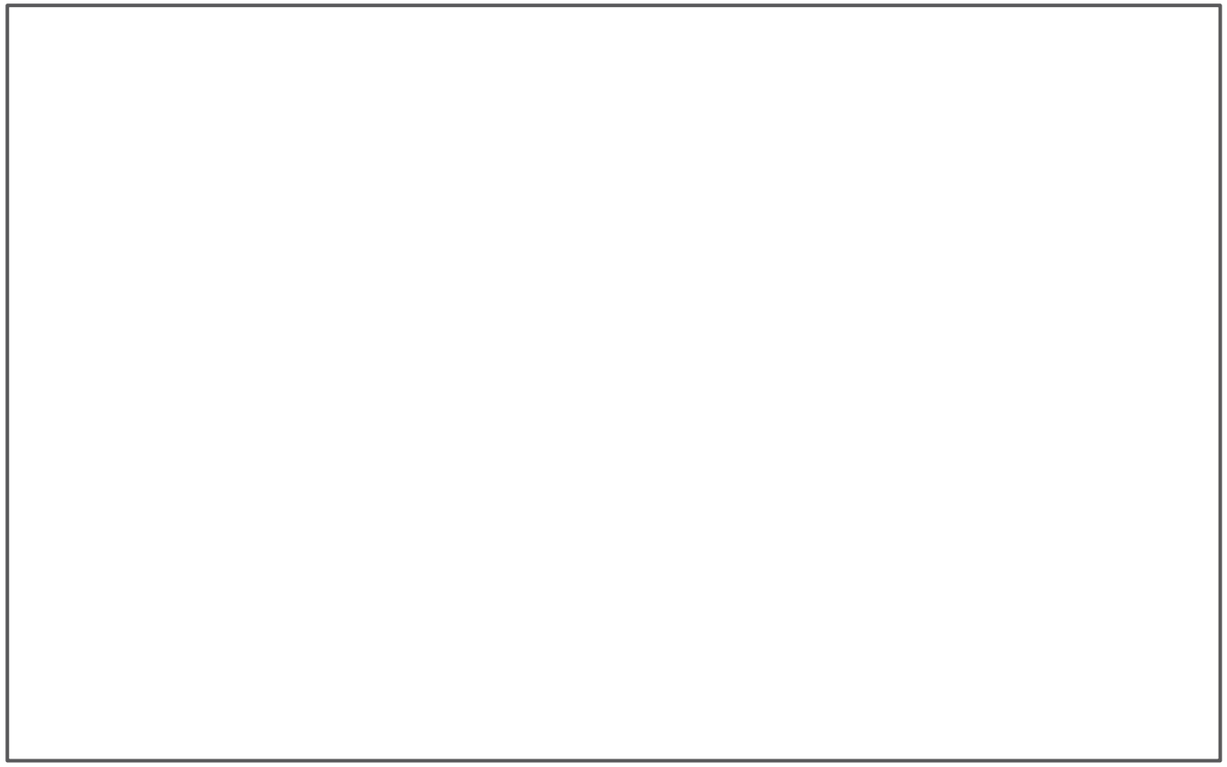
"La tragedia de Hamlet, príncipe de Dinamarca (título original en inglés: The Tragedy of Hamlet, Prince of Denmark), o simplemente Hamlet, es una tragedia del dramaturgo …"

ChatGPT, personal communication, February 11, 2023

Introduction

How does machine learning work in chemistry?

Data in



Science **2018**, *360*, 186

Introduction

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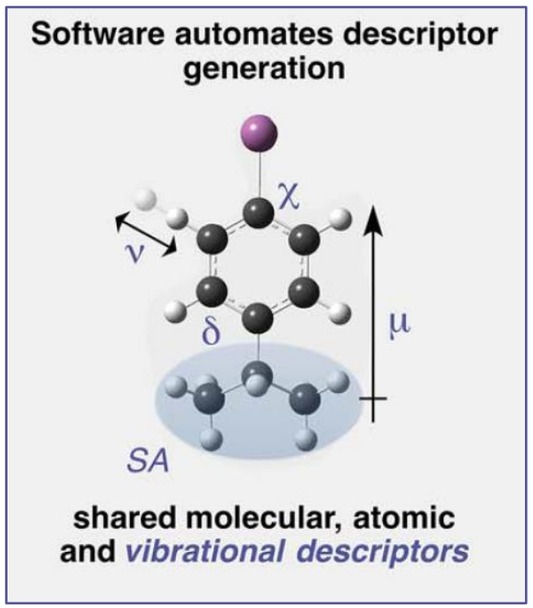

Molecular properties

- *Solubility*
- *b.p.*

Atomic properties

- *Charge*
- *Sterics*

Material properties

- *Component ratio*

Process properties

- *Temperature*
- *Pressure*

Science **2018**, *360*, 186

Introduction

How does machine learning work in chemistry?

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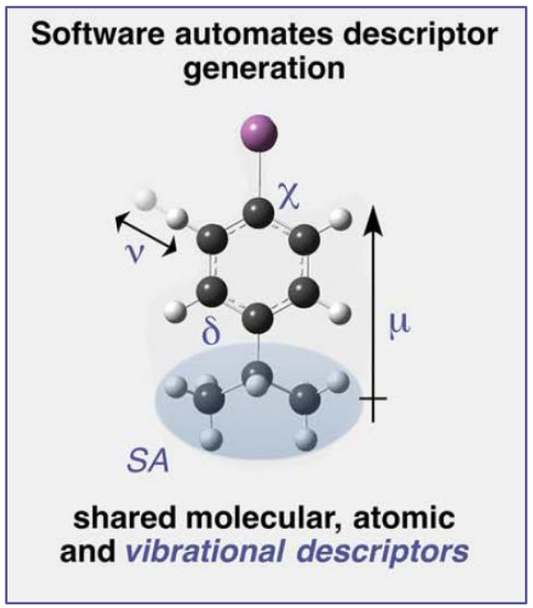

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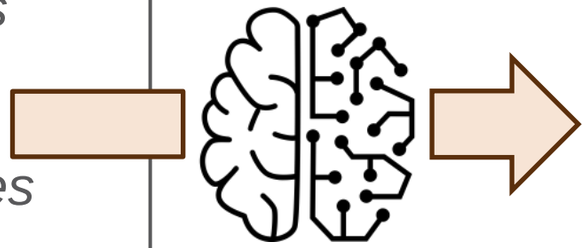

Science **2018**, *360*, 186

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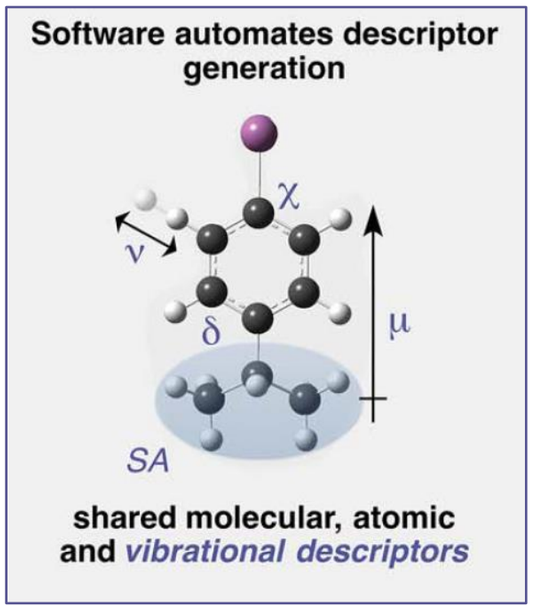

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Design an effective catalyst

Design an optimal solar cell

Science **2018**, *360*, 186

Introduction

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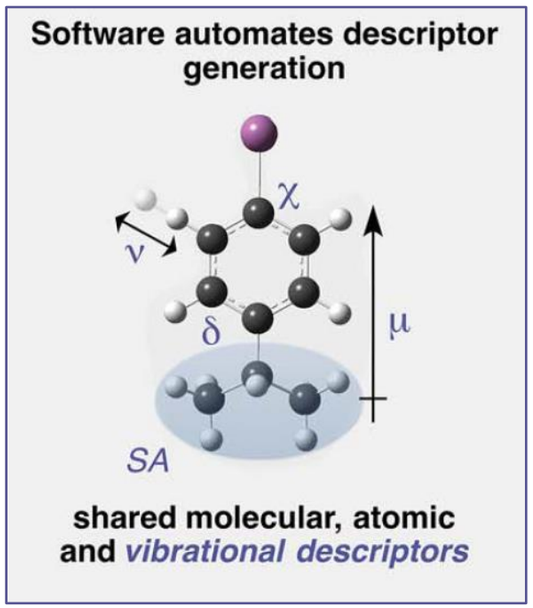

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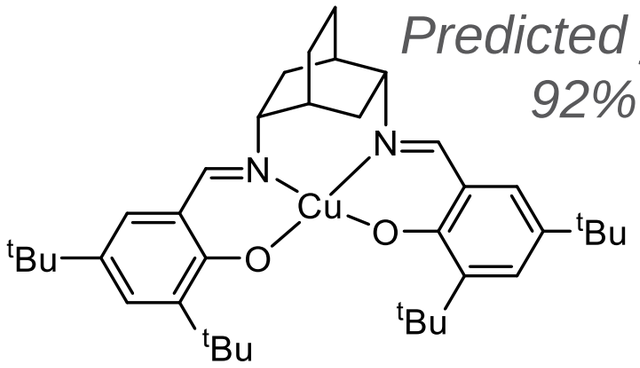

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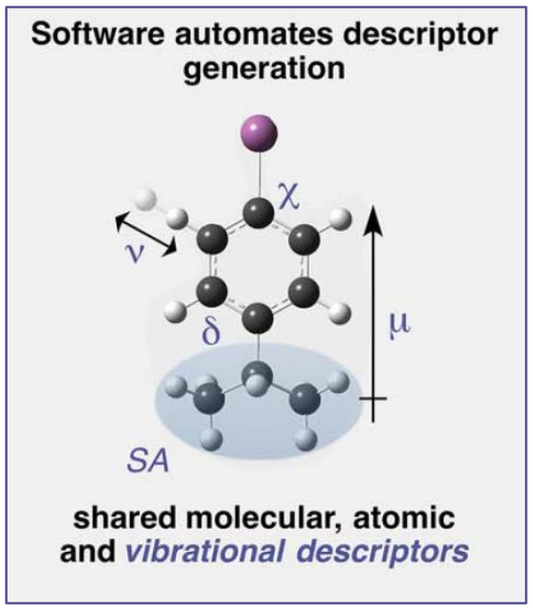

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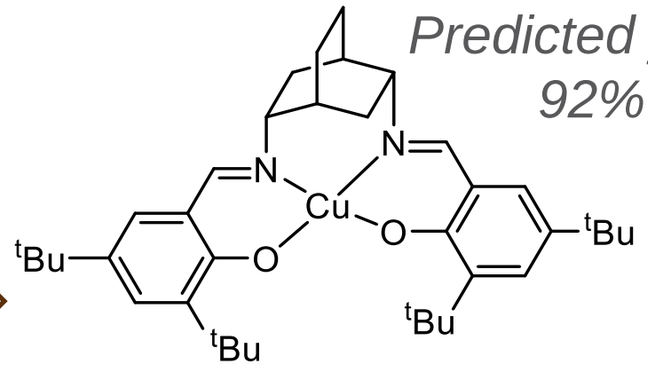


Predicted yield: 92%

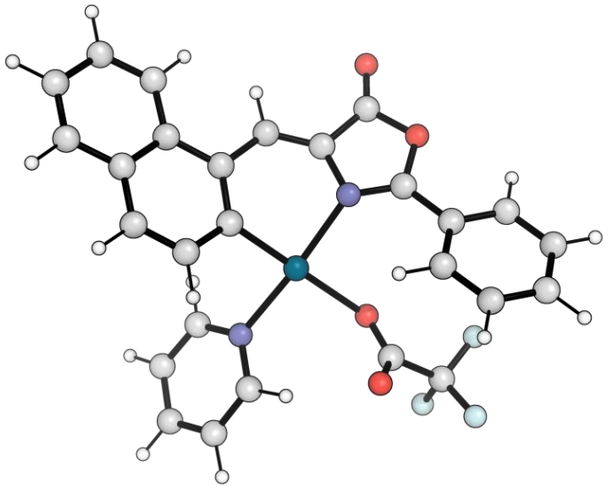
20% graphene + 40% Si + 40% GaAs

Predicted solar-cell efficiency: 21%

Science **2018**, *360*, 186

Introduction

Machine learning (Why in chemistry?)



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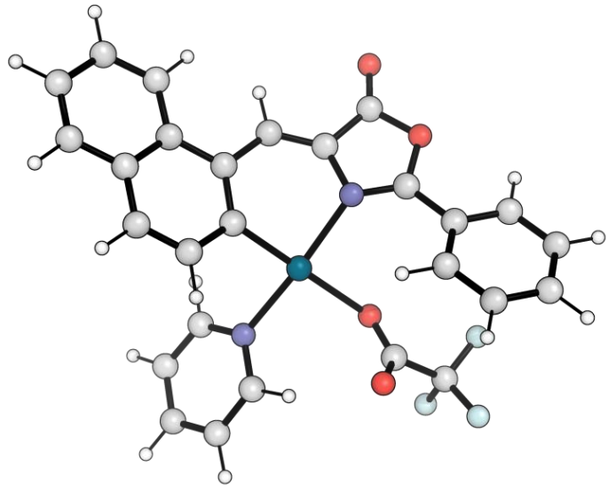
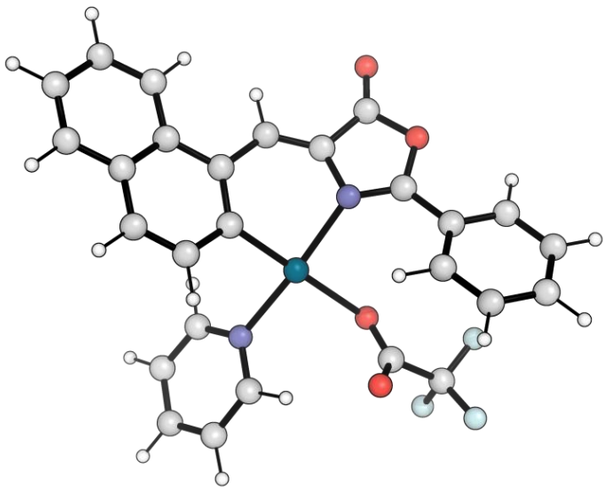
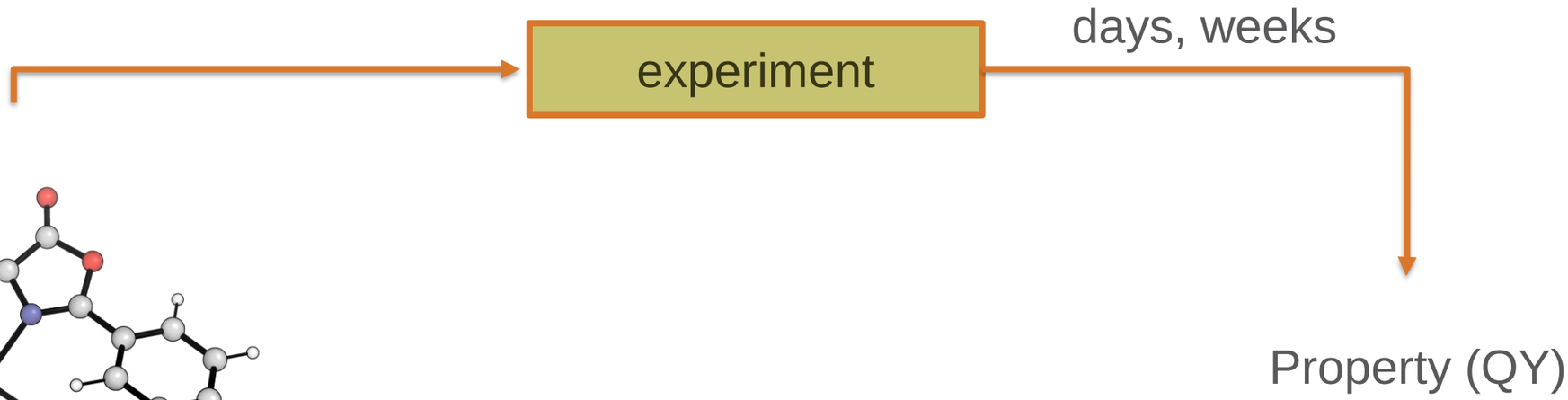


Property (QY)

Introduction

Machine learning (Why in chemistry?)





Introduction

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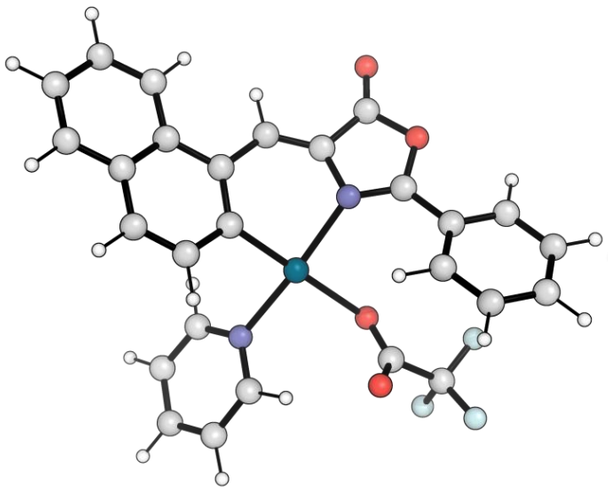


experiment

days, weeks

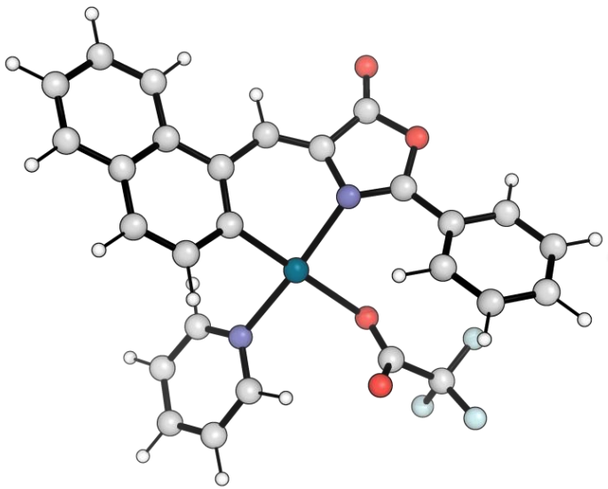
$H\Psi = E\Psi$

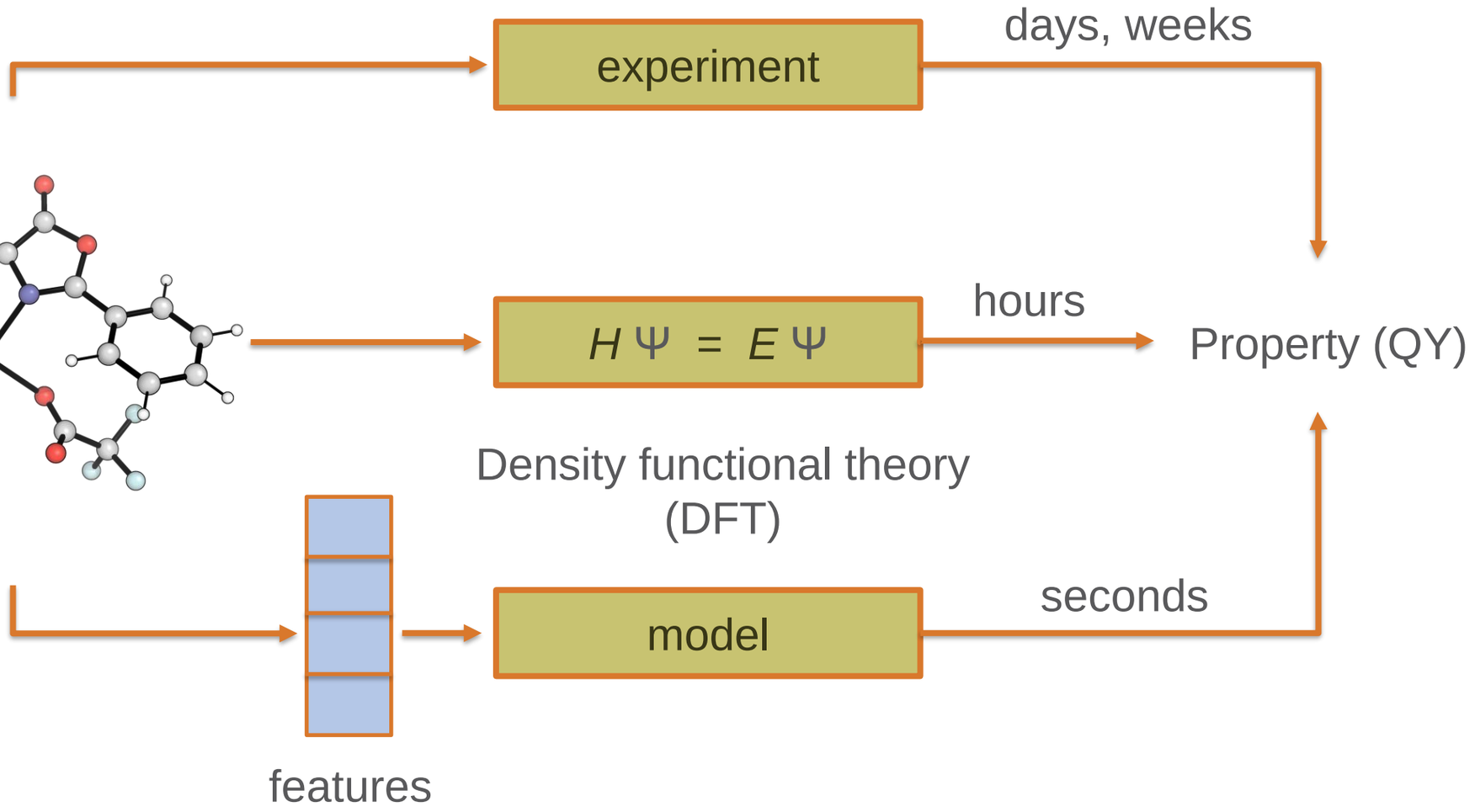
hours

Property (QY)

Density functional theory
(DFT)

Machine learning (Why in chemistry?)





Introduction

ChemCrow

Input your OpenAI API key.

••

Available tools: 12

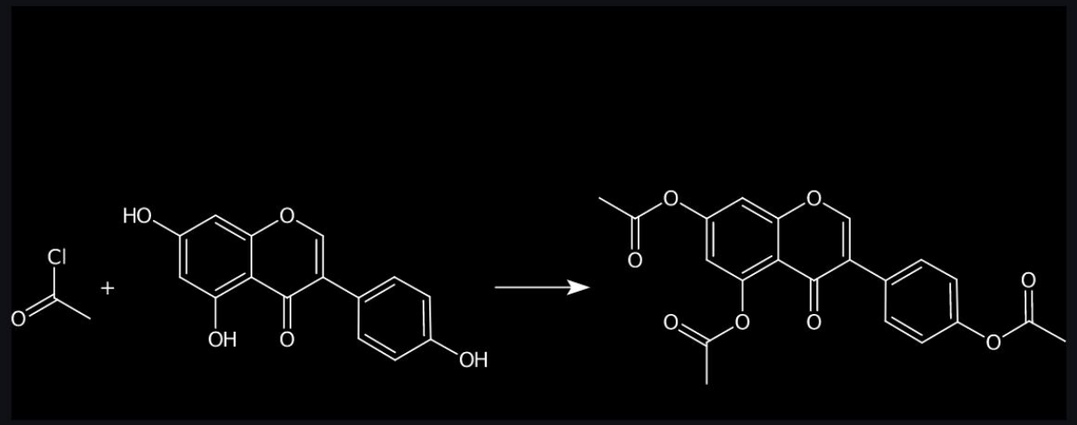
Tool	Description
PatentCheck	Input SMILES, returns if molecule is patente
MolSimilarity	Input two molecule SMILES (separated by '.')
SMILES2Weight	Input SMILES, returns molecular weight.
FunctionalGroups	Input SMILES, return list of functional group

✅ **RXNPredict:** O=c1c(-c2ccc(O)cc2)coc2cc(O)cc(O)c12.CC(=O)Cl

The reaction of phytic acid with acetyl chloride does not seem to produce any new product, as the output SMILES is the same as the input for phytic acid. Now, I will predict the product of genistein with acetyl chloride.

Action: RXNPredict
Action Input: O=c1c(-c2ccc(O)cc2)coc2cc(O)cc(O)c12.CC(=O)Cl

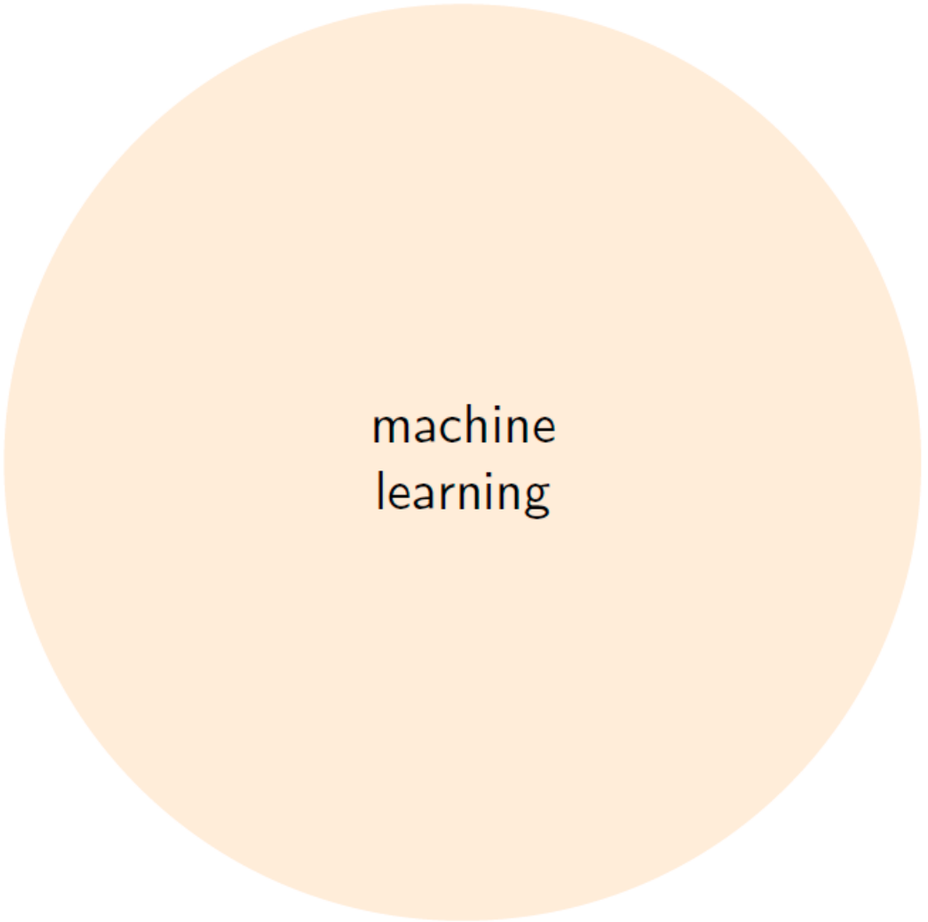
CC(=O)Oc1ccc(-c2coc3cc(OC(C)=O)cc(OC(C)=O)c3c2=O)cc1



Your message

[ur-whitelab/chemcrow-public: Chemcrow]

Types of machine learning



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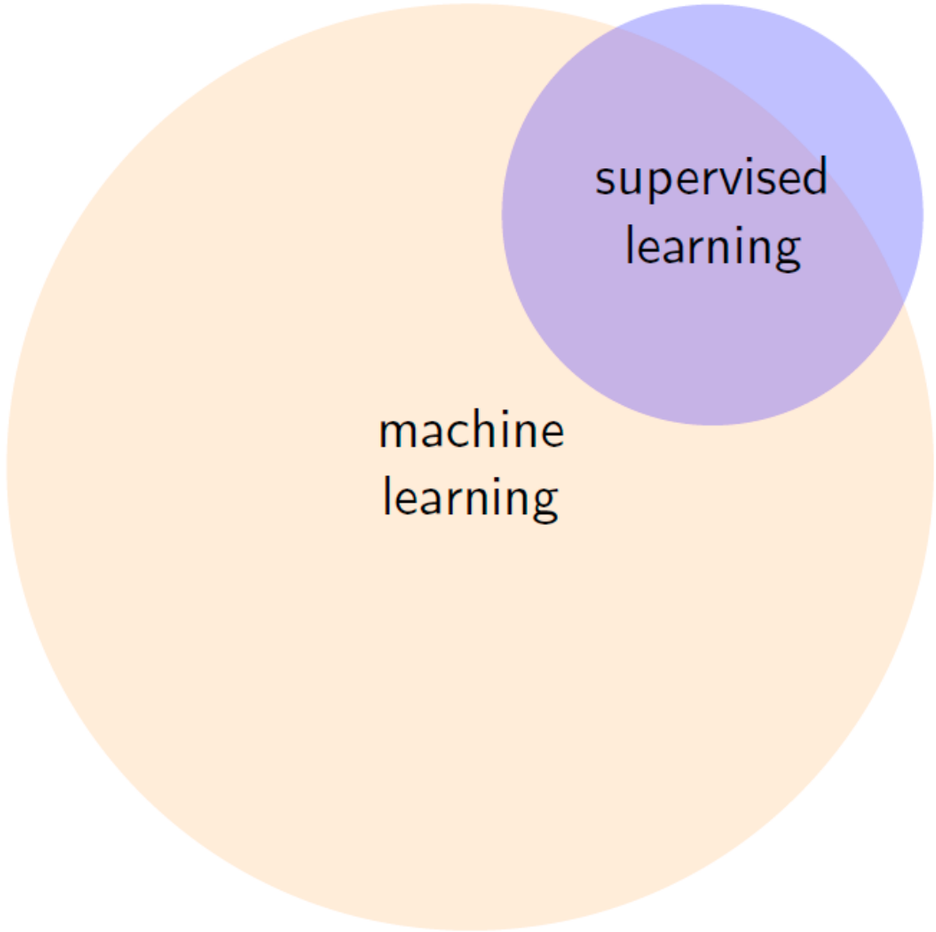

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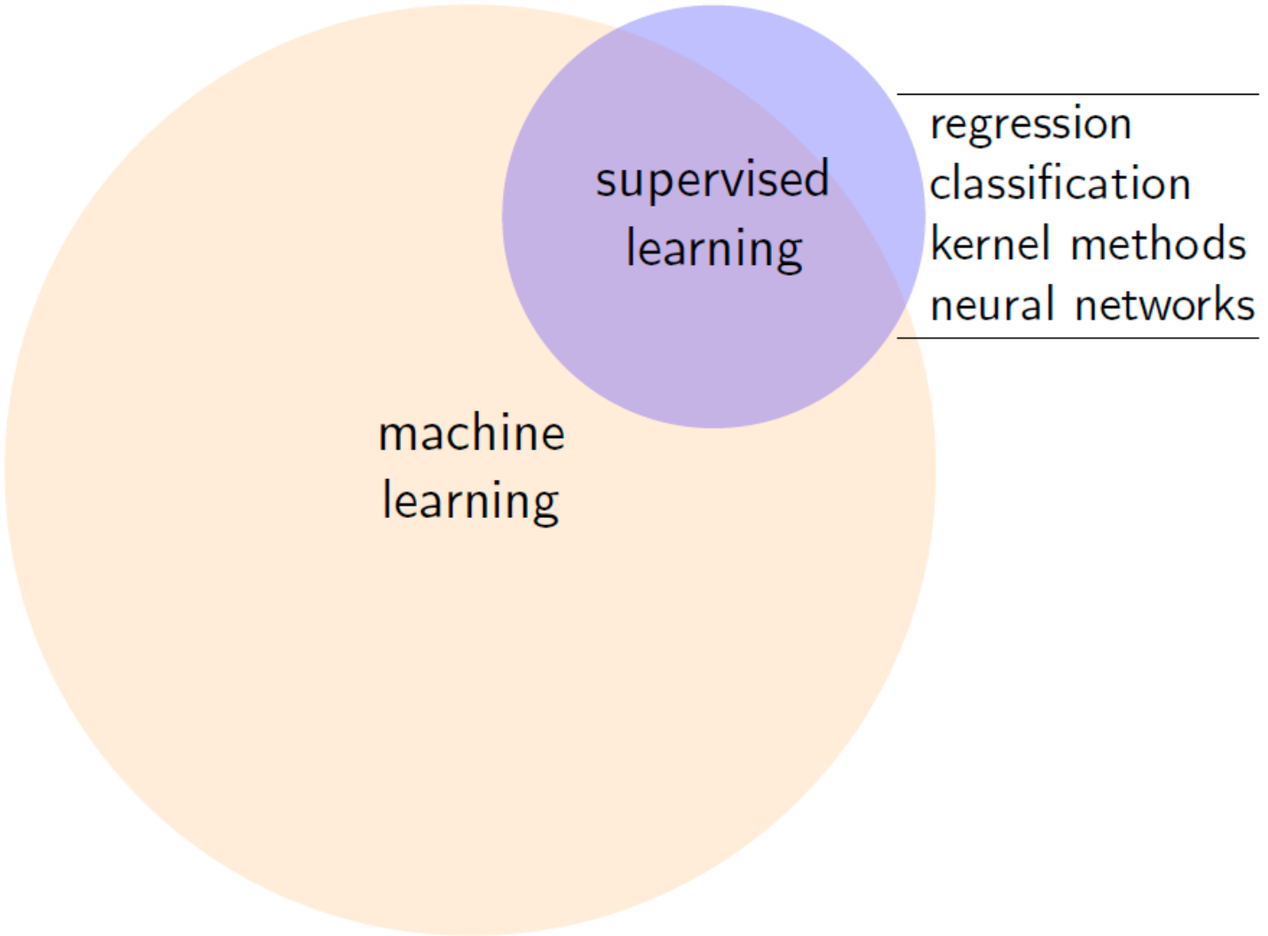

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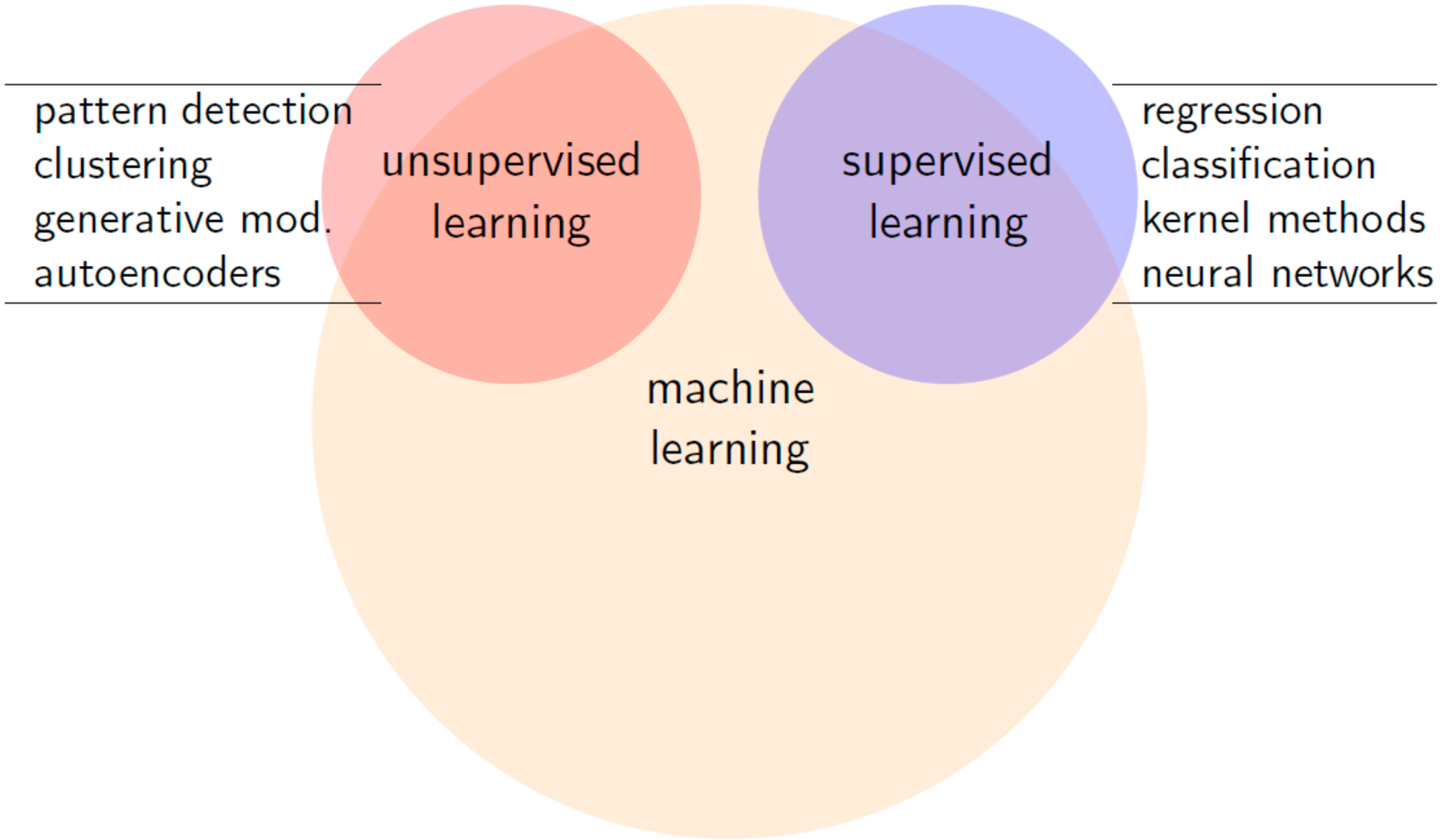

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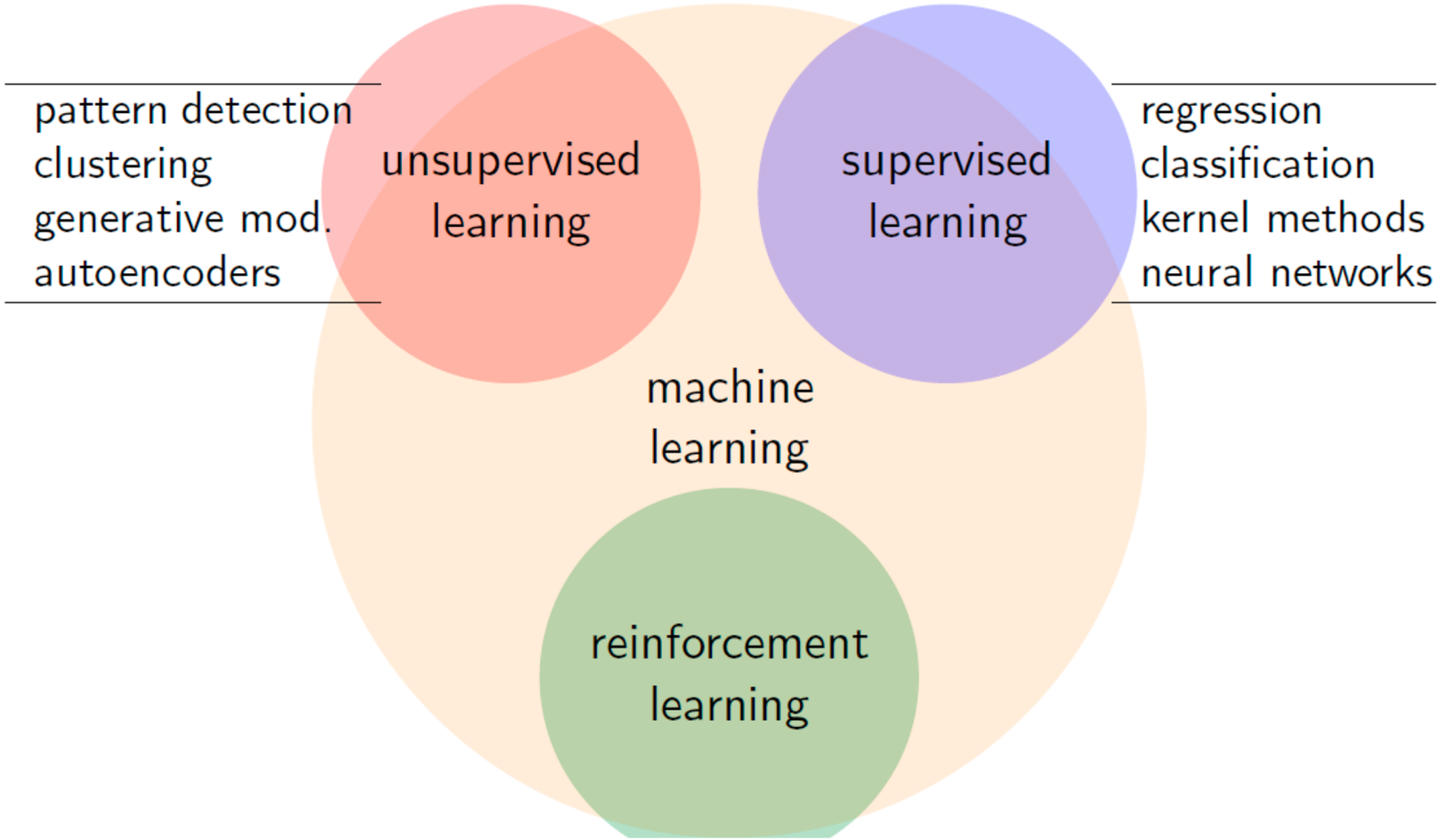

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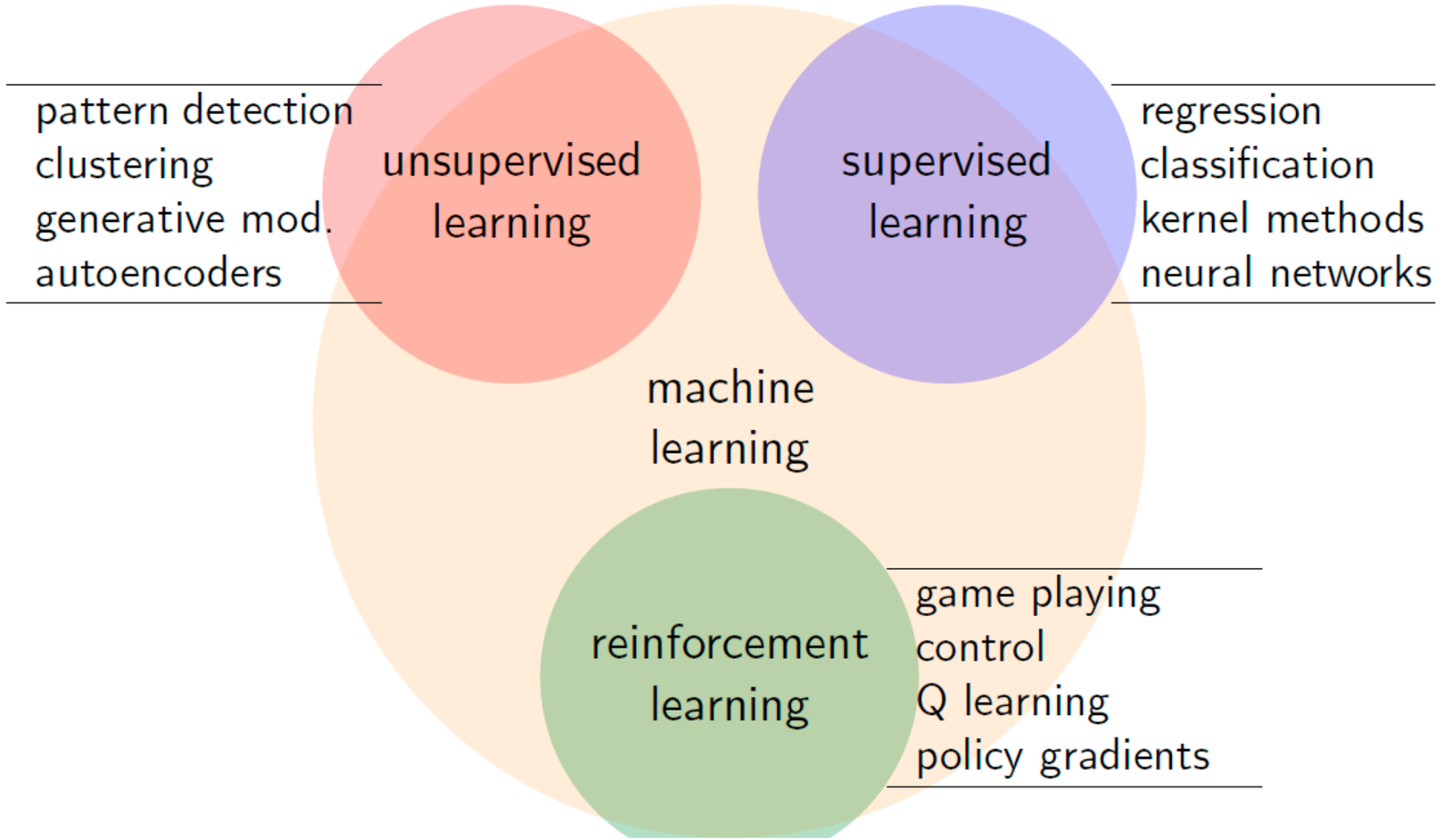
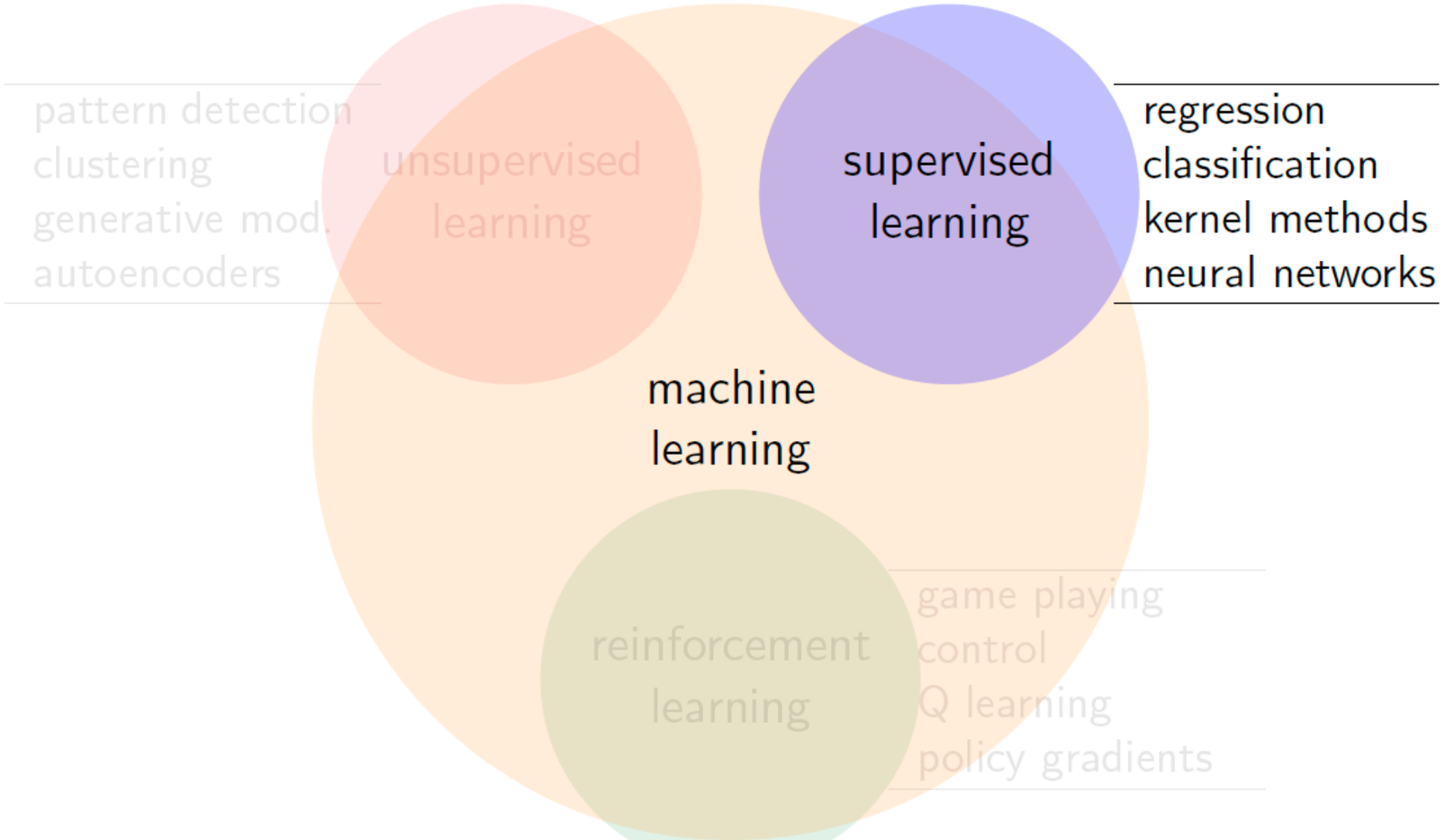
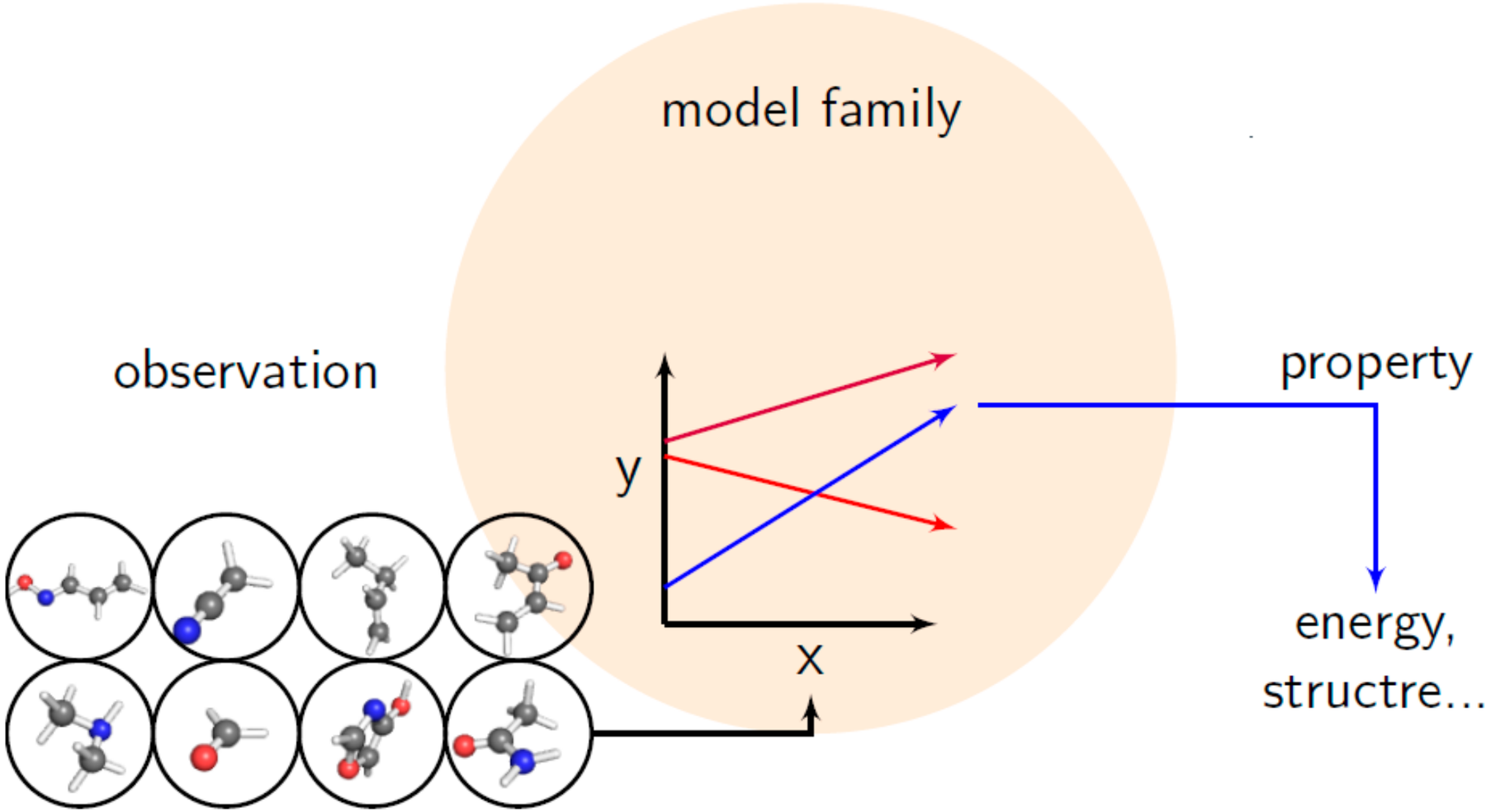


Introduction

Types of machine learning

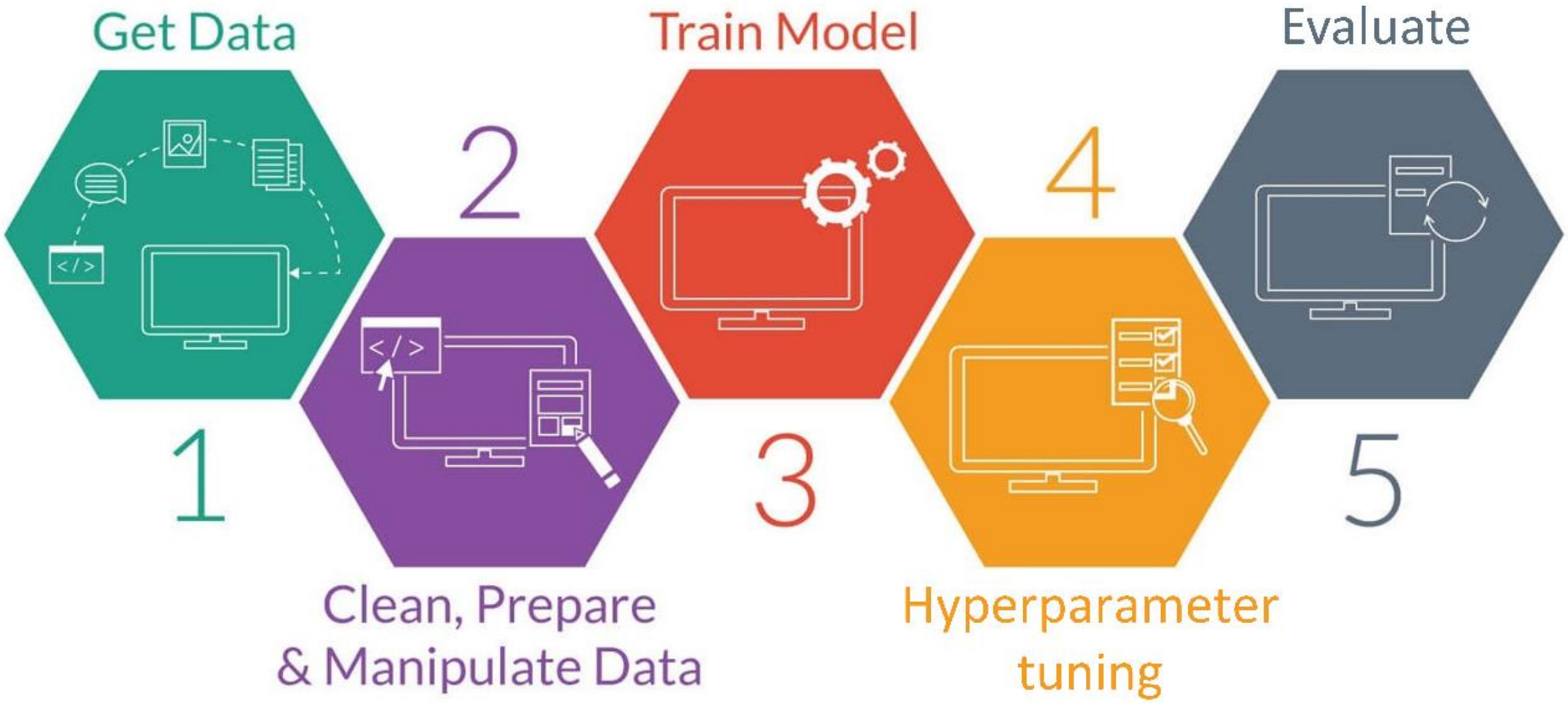


The goal of supervised learning



Introduction

ML workflow



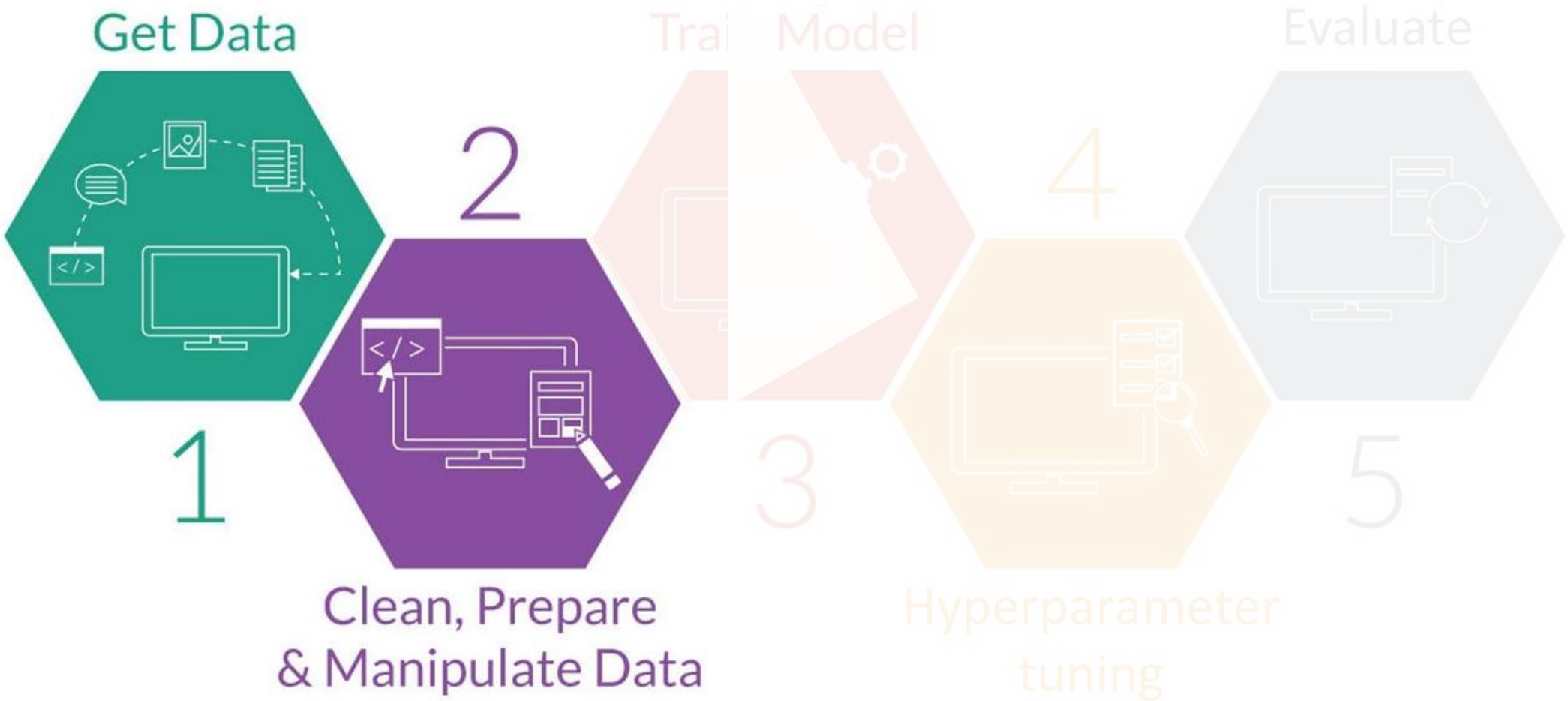
Why applied ML is so challenging

Because it requires expertise about ML and the target problem.

- Choose the right framing for inputs and outputs of problem
  Some unknown but coherent relationship is required between inputs and outputs.
- Collect the good training data
- Assess the quality of data (quality control)
- Choose the relevant representation for inputs
- Choose the right algorithm for ML
  ML approximate an unknown underlying mapping function from inputs to outputs.
- Choose the right algorithm configuration
- Test thoroughly whether the ML prediction works well

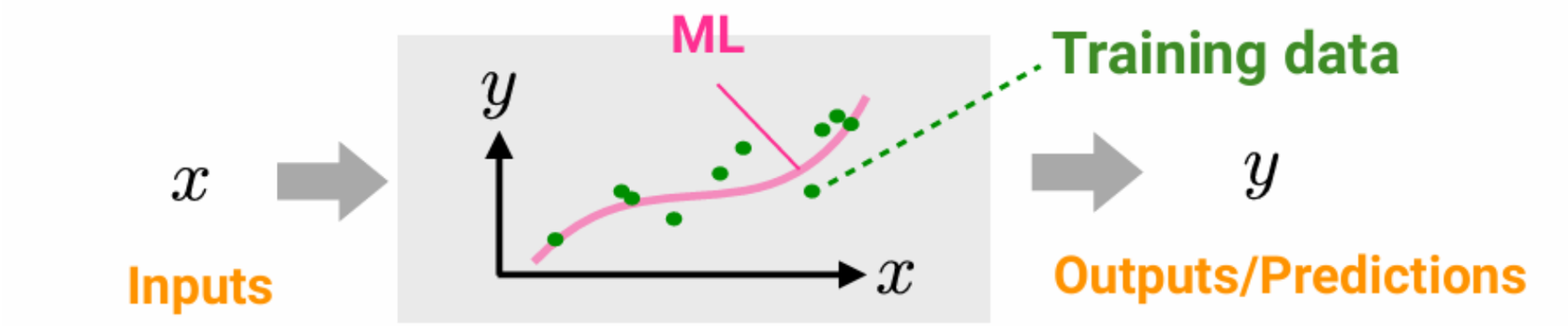
Introduction

ML workflow



Introduction

Remember the quality of your inputs decide the quality of your output



- The computer sees only the data you give it
- "ML is interpolating the training data" means that when the training data is poor-quality or very biased, so is the ML prediction no matter what state-of-the-art ML method is used.
- In other words, **"data-driven" means that prediction is defined by the data itselves in the first place.** All other factors, including what ML models should be used, are secondary issues.
- A first key to success is collecting good training data.

https://itakigawa.github.io/hsi2020/

Introduction

“Garbage in, garbage out”

Introduction

“Garbage in, garbage out”

Data

Introduction

“Garbage in, garbage out”

Data

\+ Generative AI =

Introduction

“Garbage in, garbage out”

Data

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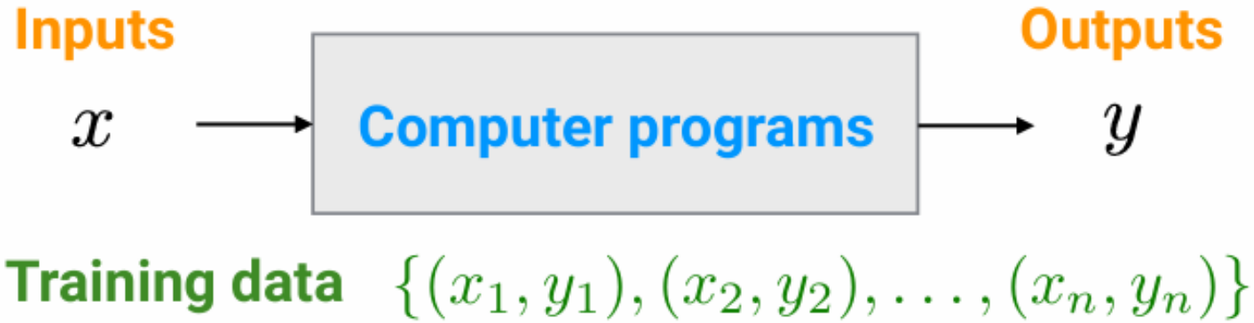
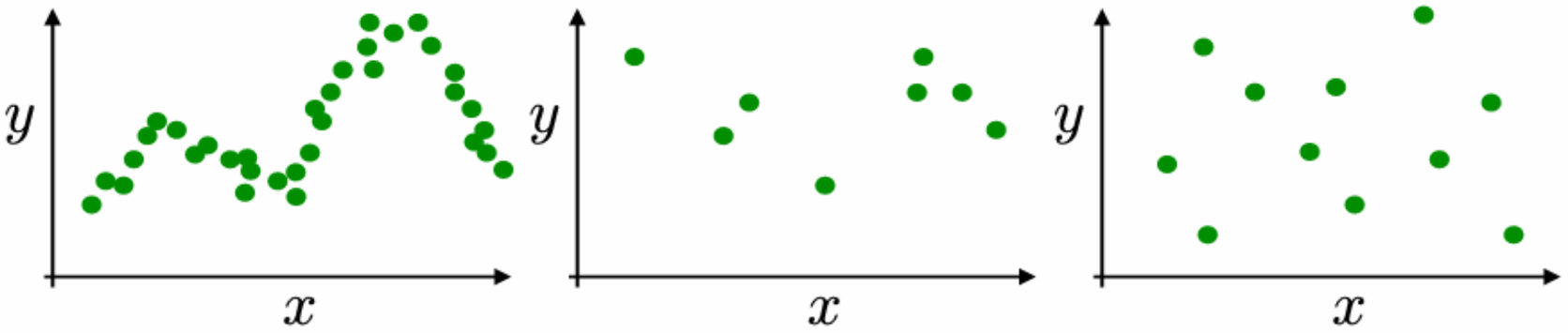
Introduction

“Garbage in, garbage out”





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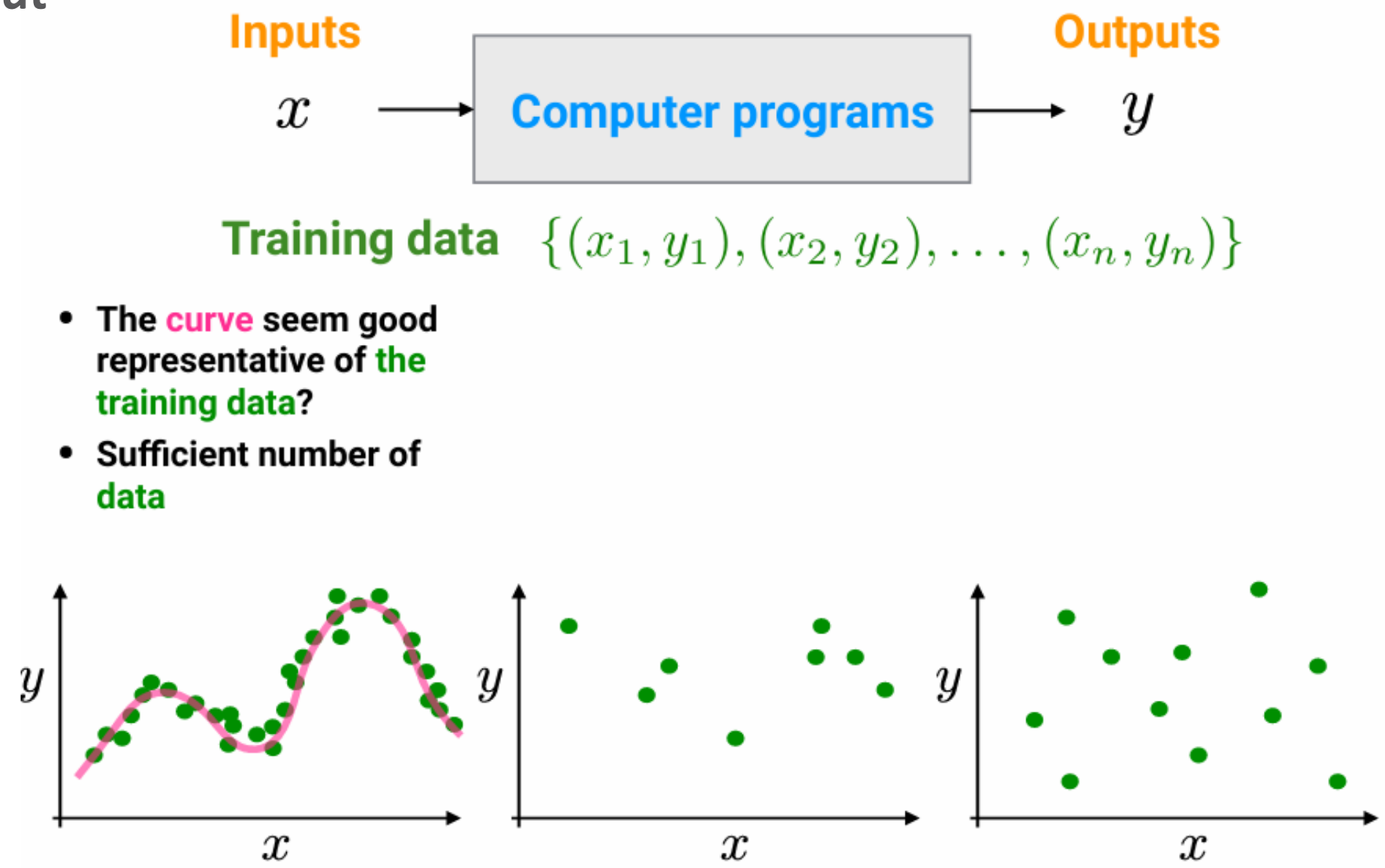

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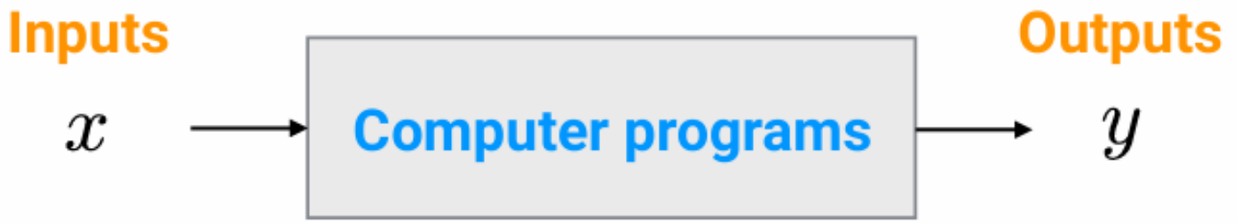
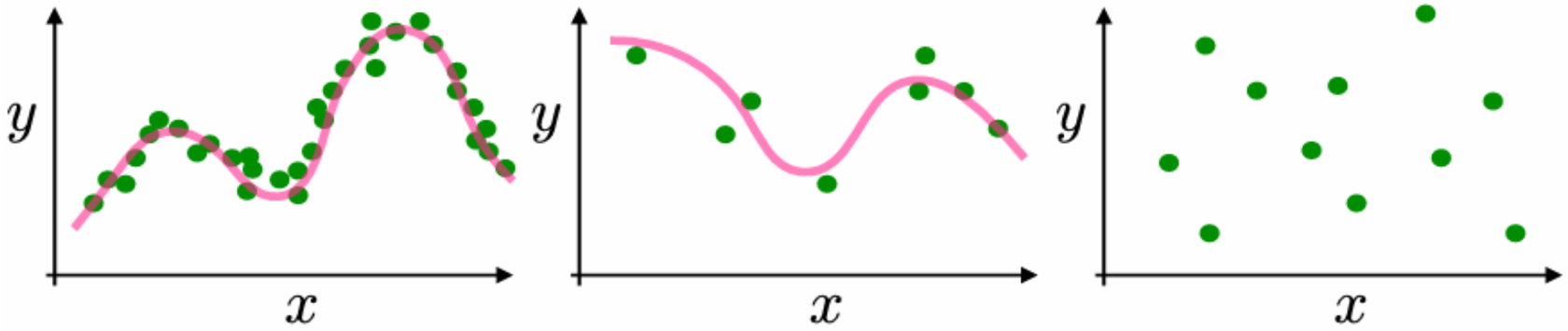
"Garbage in, garbage out"



Training data $\{(x_1, y_1), (x_2, y_2), \ldots, (x_n, y_n)\}$

- The curve seem good representative of the training data?
- Sufficient number of data

- What you you think about this case?
- So so, but too early to say something due to the small number of data?



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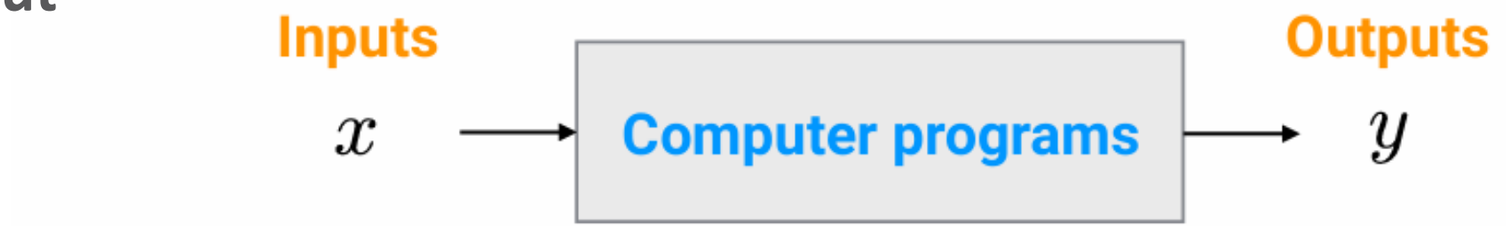

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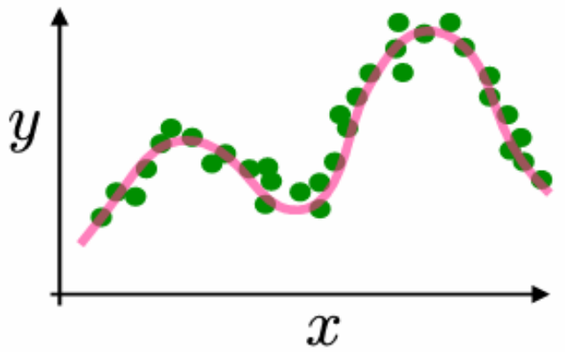

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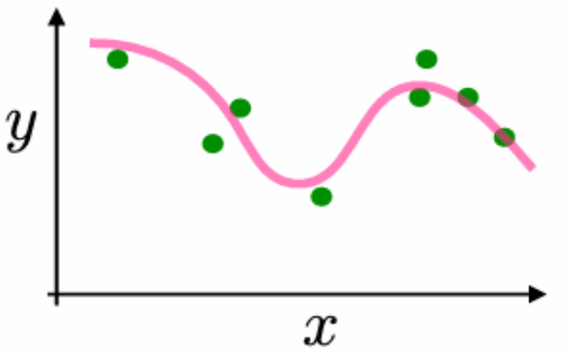
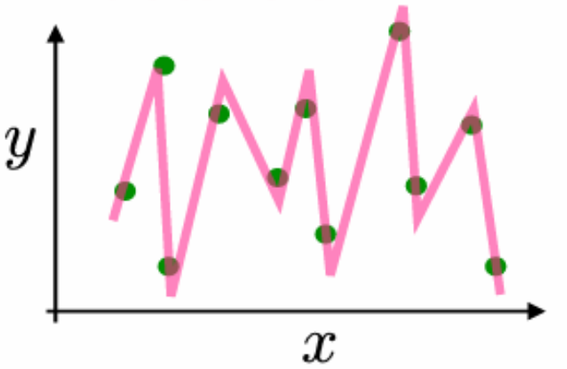


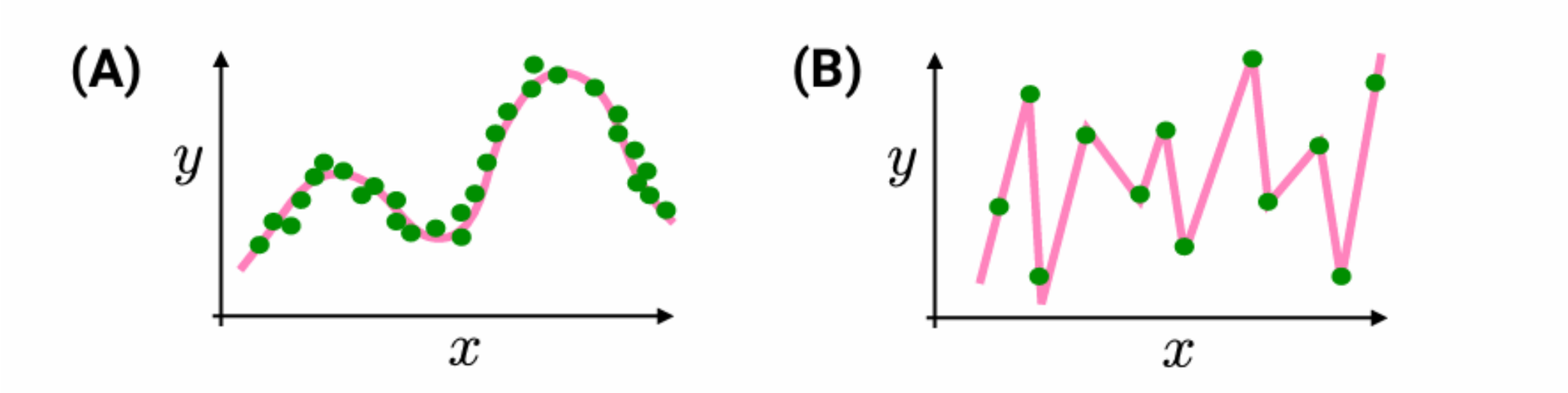
- Hopelessly invalid
- No correlation observed between inputs and outputs
- Problem is the data, not the curve form



Introduction

But how can we evaluate the ML prediction?

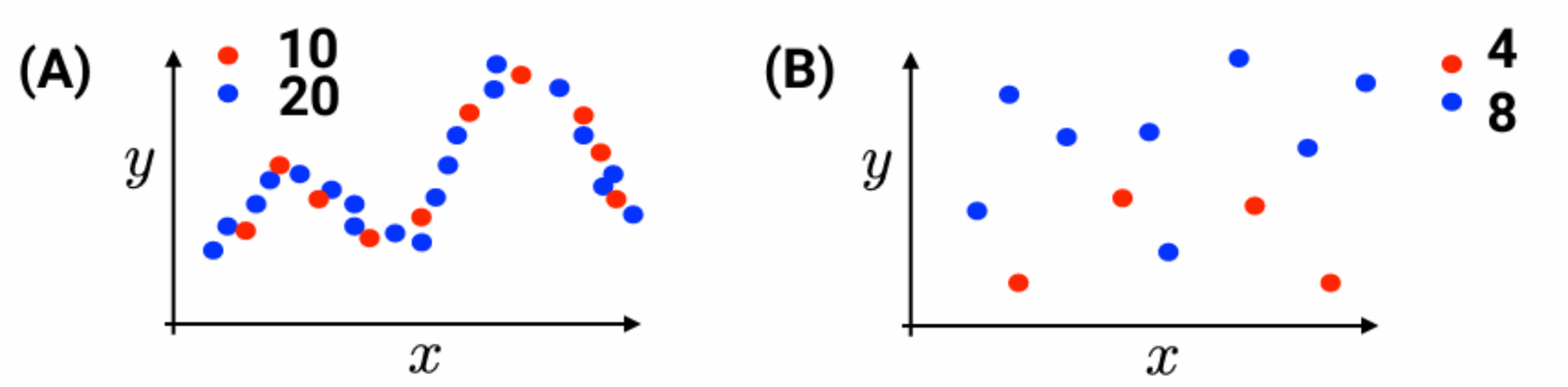
How can we quantitavely know that curve fitting (A) is good but (B) is bad?

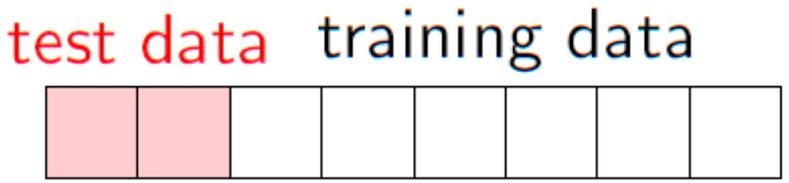


It seems that the prediction errors of (B) are even much smaller tan (A)…

Training data and test data

We hold out some (say 1/3) of the data as the test data





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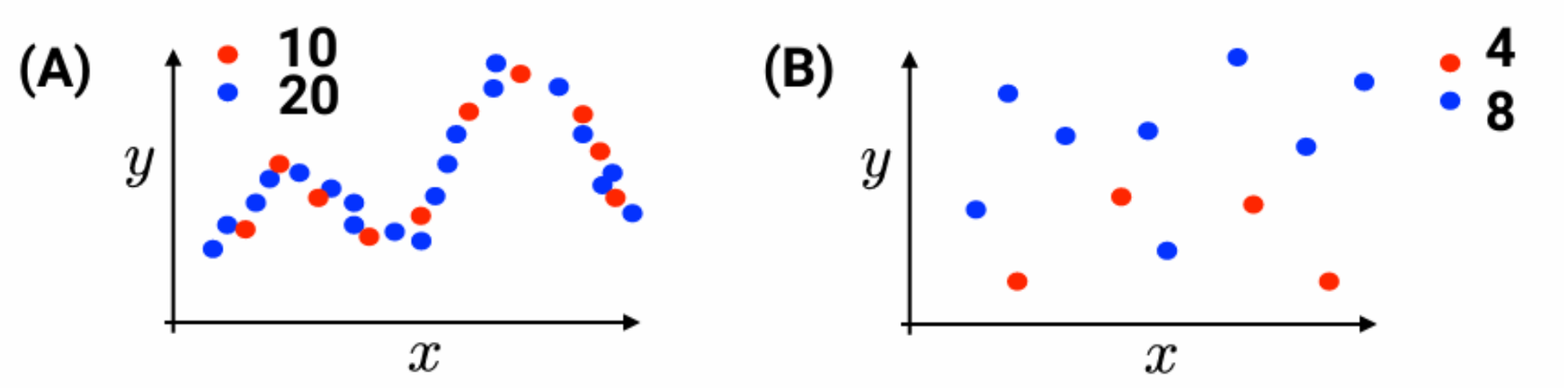
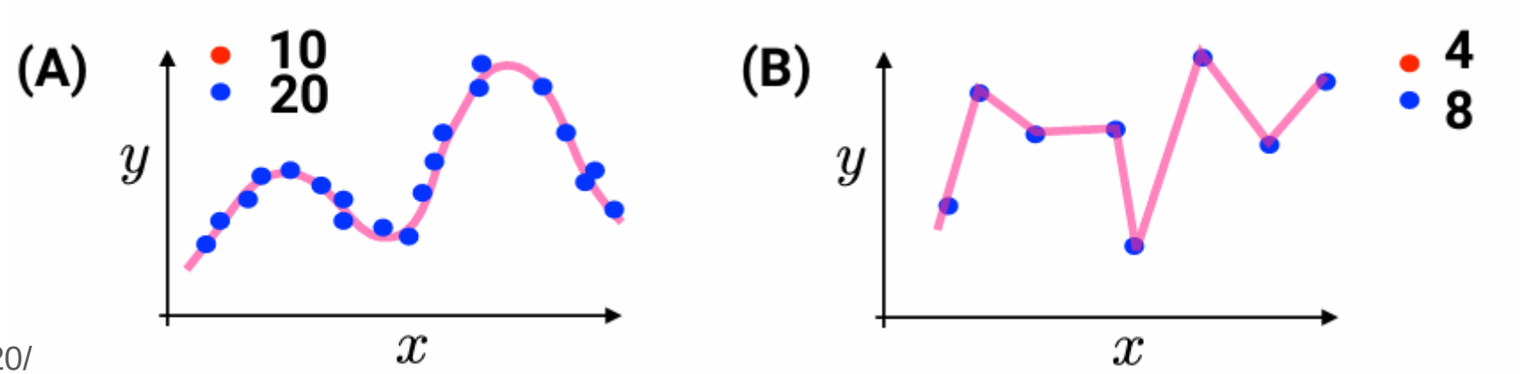


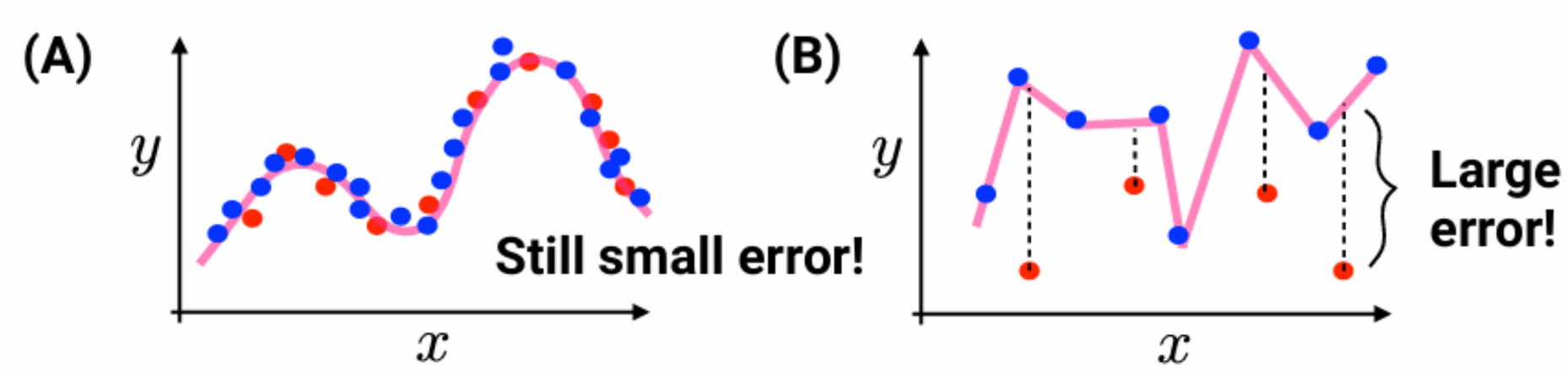
Apply ML to the remaining training data, and obtain the prediction curve



Introduction

The performance evaluated by training-test split

Test how the predictions by curve are accurate using the test data



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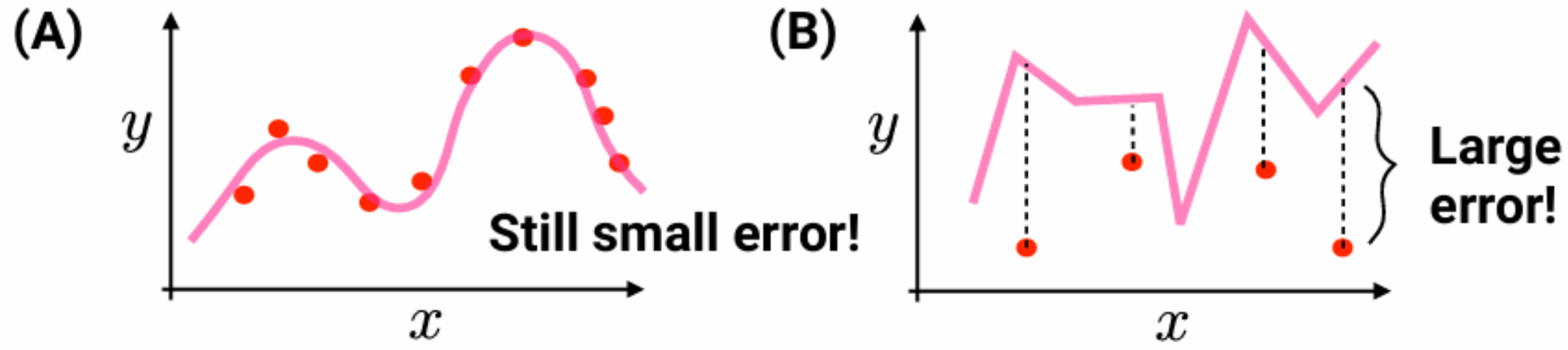
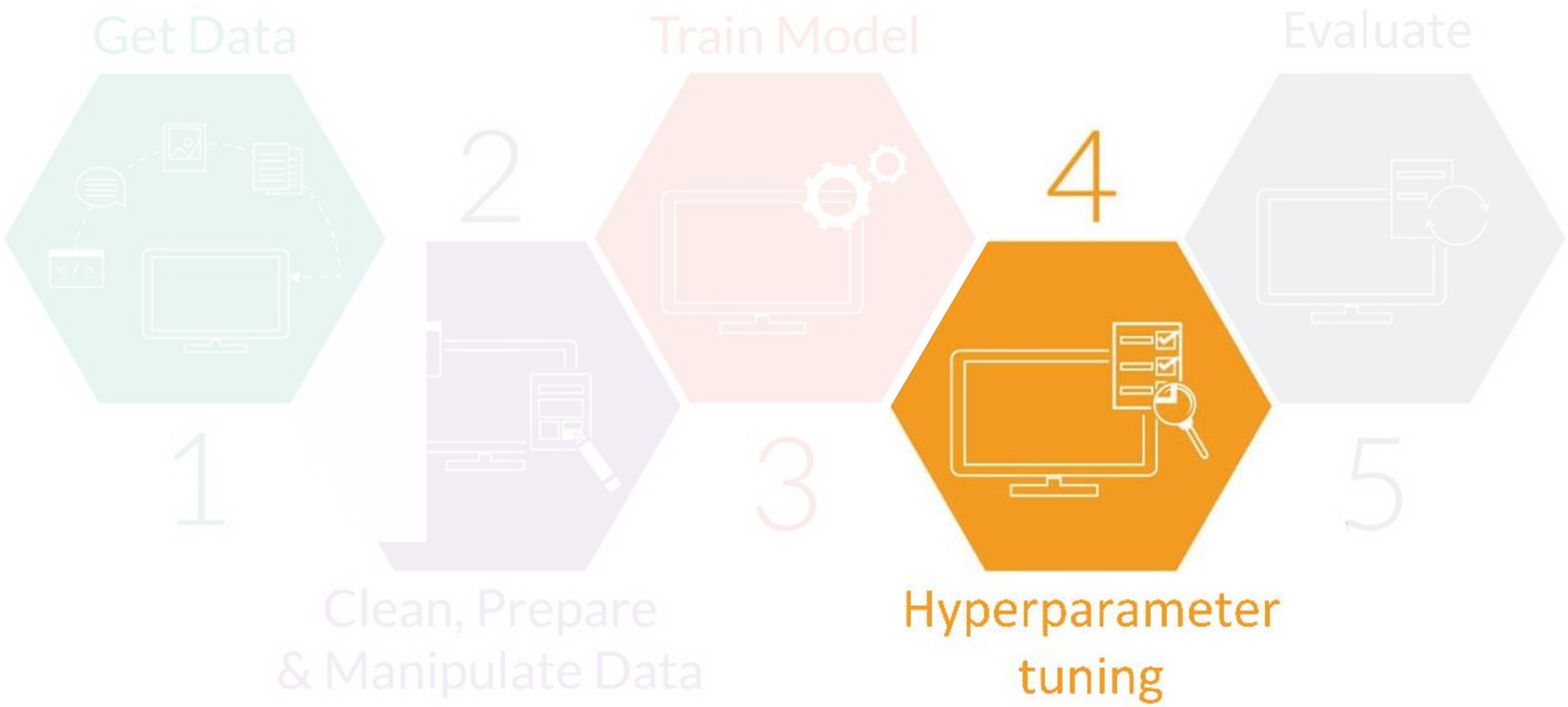


- The performance of ML should be measured by the “test error”.
- Note that making the training errors zero is easy. Just memorize the training data.
- In well-posed situations, the test errors are always larger than the training error.
- Ideally, both training errors and test errors are small.

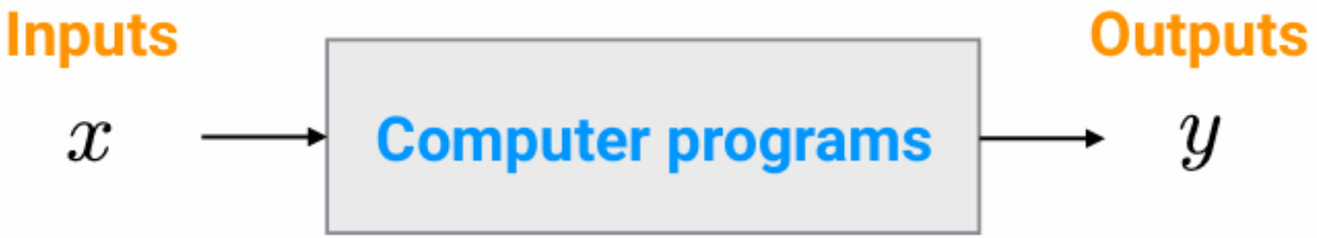
Introduction

ML workflow



Introduction

Training / validation / test split



Available data $\{(x_1, y_1), (x_2, y_2), \ldots, (x_n, y_n)\}$

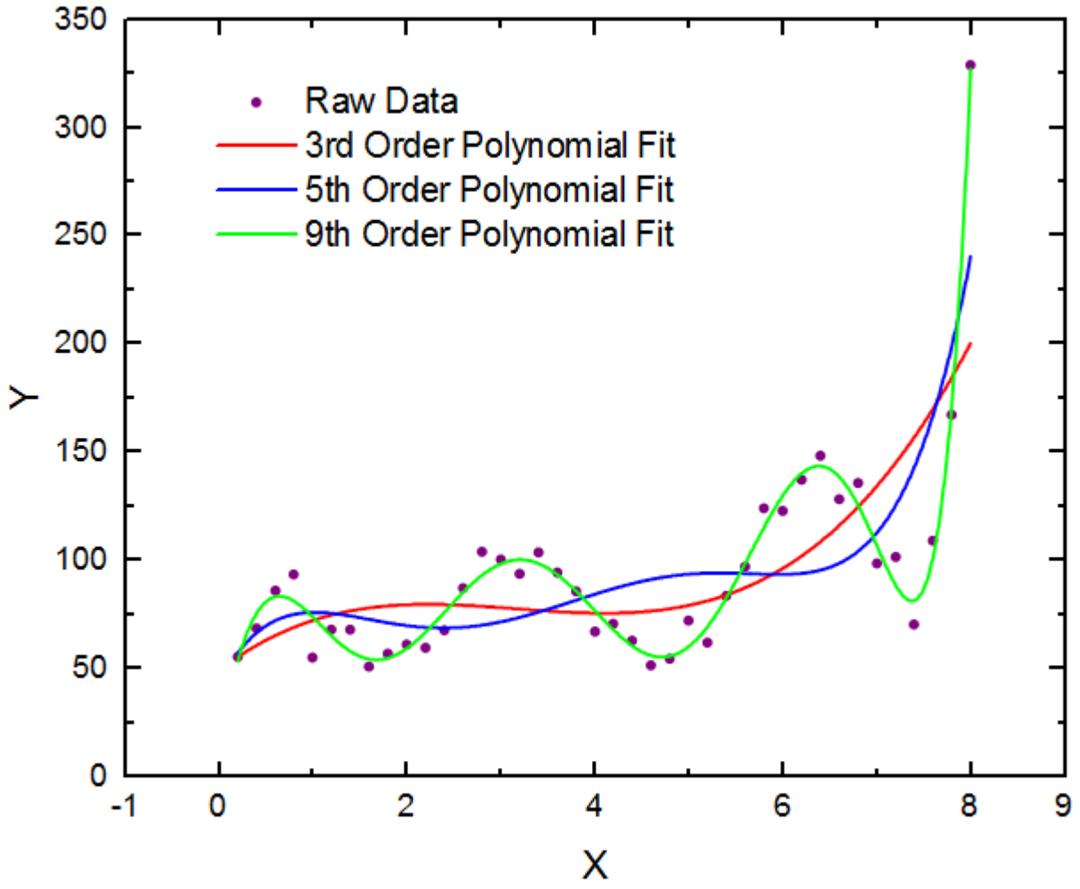
Training data — **Used for "model training (fitting)"**

Validation data — **Used for "hyperparameter tuning" (or "model selection")**

Test data — **Used for evaluating the prediction performance**

Introduction

Hyperparameters



When we try to fit polynomial functions:

$$\hat{y} = \beta_0 + \beta_1 x + \beta_2 x^2 + \cdots + \beta_p x_p^p$$

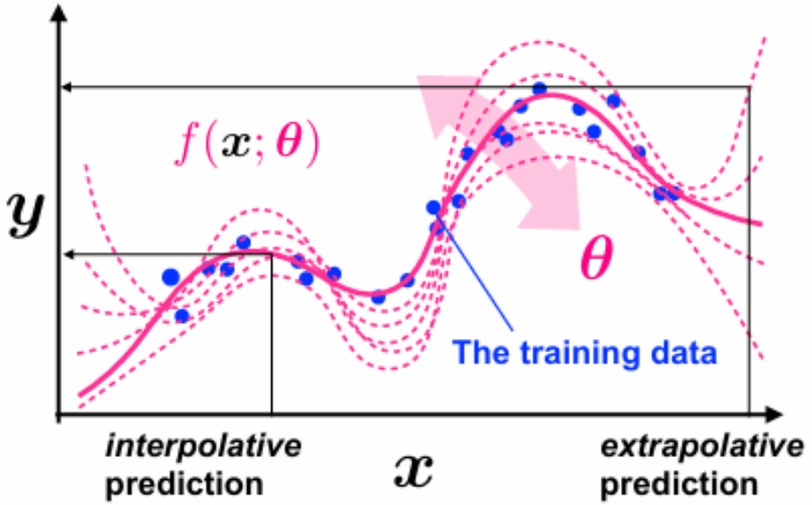
Parameters: $\beta_0, \beta_1, \ldots, \beta_p$ (coefficients)

Hyperarameters: p (order of polynomials)

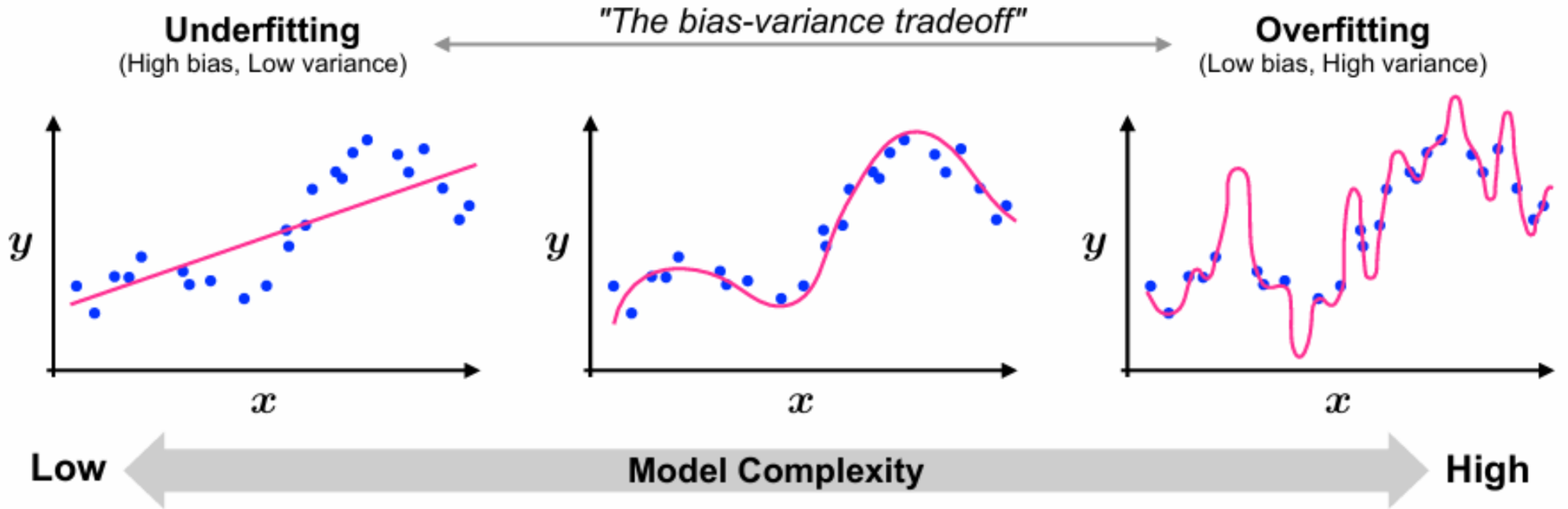
Introduction

A function $f(x;\theta)$ best fitted to
a given set of example input-output pairs
(the training data).

$\{(x_1, y_1), (x_2, y_2), \ldots, (x_n, y_n)\}$

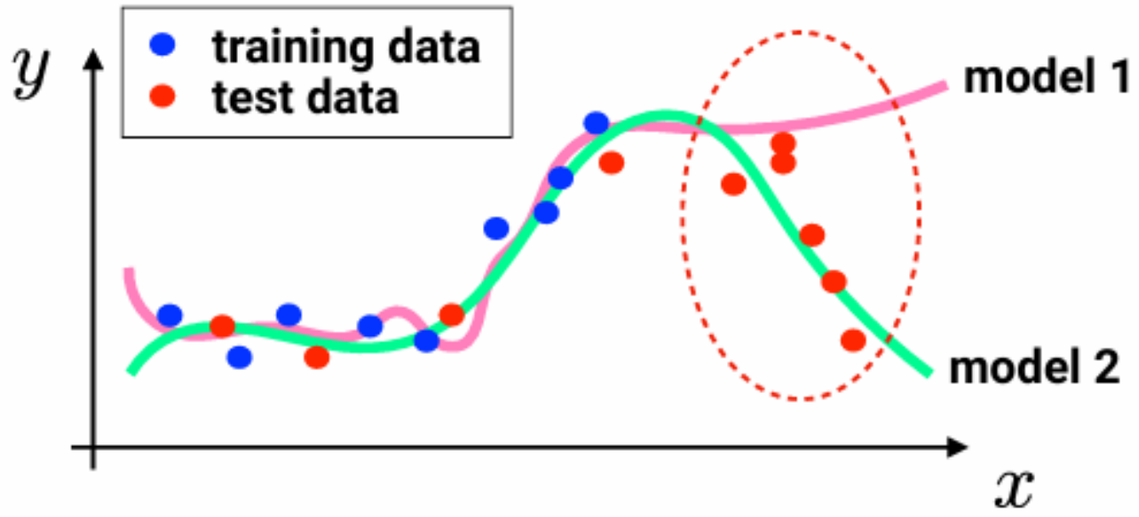


(High-dimensional)



Needs for “validation” data

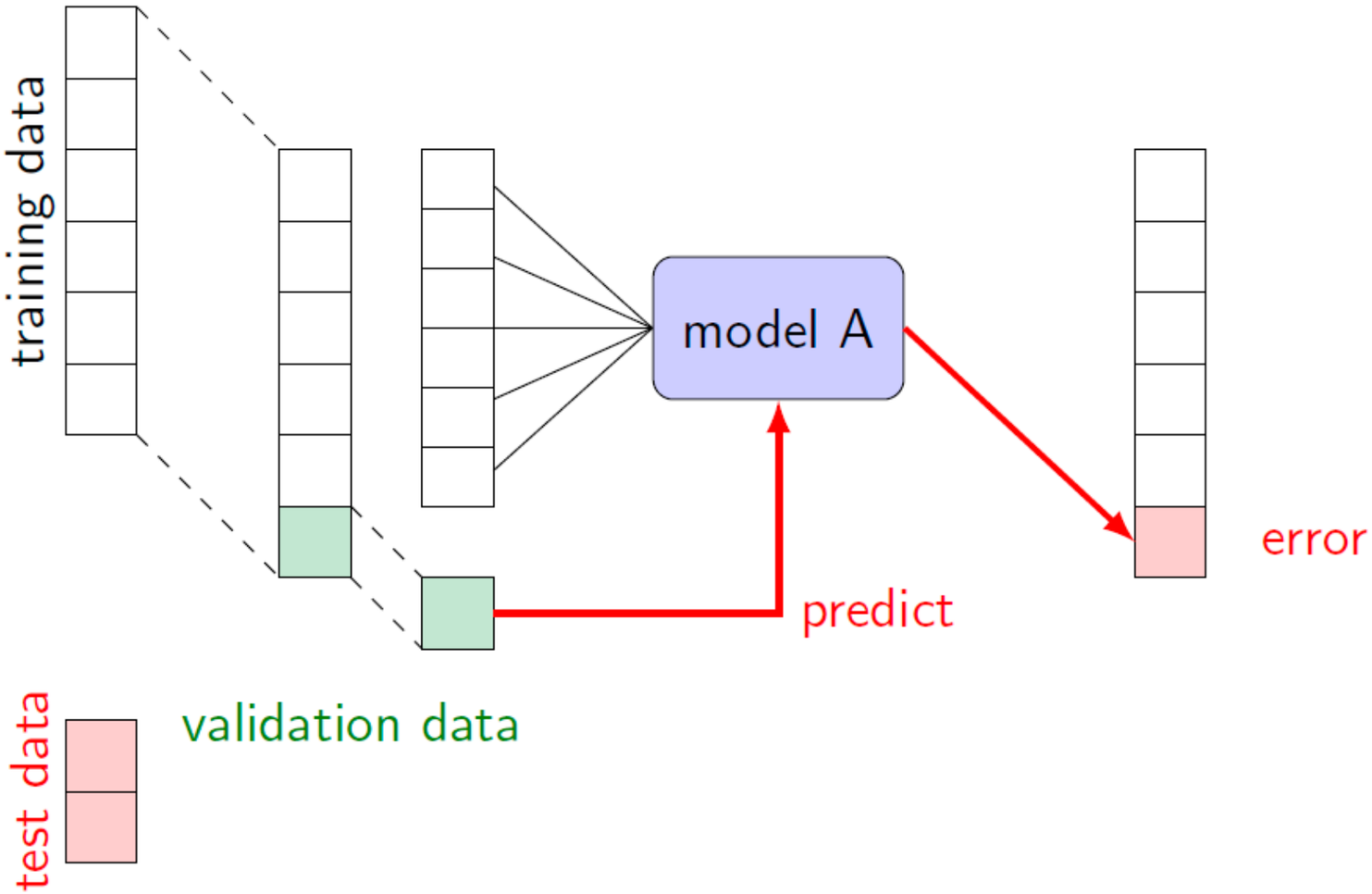
Seemingly the test data is enough also to determine which hyperparameters are good, but ...



The model 2 performs better over "test data", but this would be sort of cheating (called "data leakage")

The validation set helps us compare models like Model 1 and Model 2 without touching the test data. Only after choosing the best model using validation data do we evaluate it on the test set.

Needs for “validation” data



Introduction

“Correlation does not imply causation”

Machine learning finds any input-output correlation in high dimensions. And this does not directly mean any causation.

Introduction

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N Engl J Med 2012; 367:1562-1564

One of the most prestigious medical journal with IF(2023) 96.2

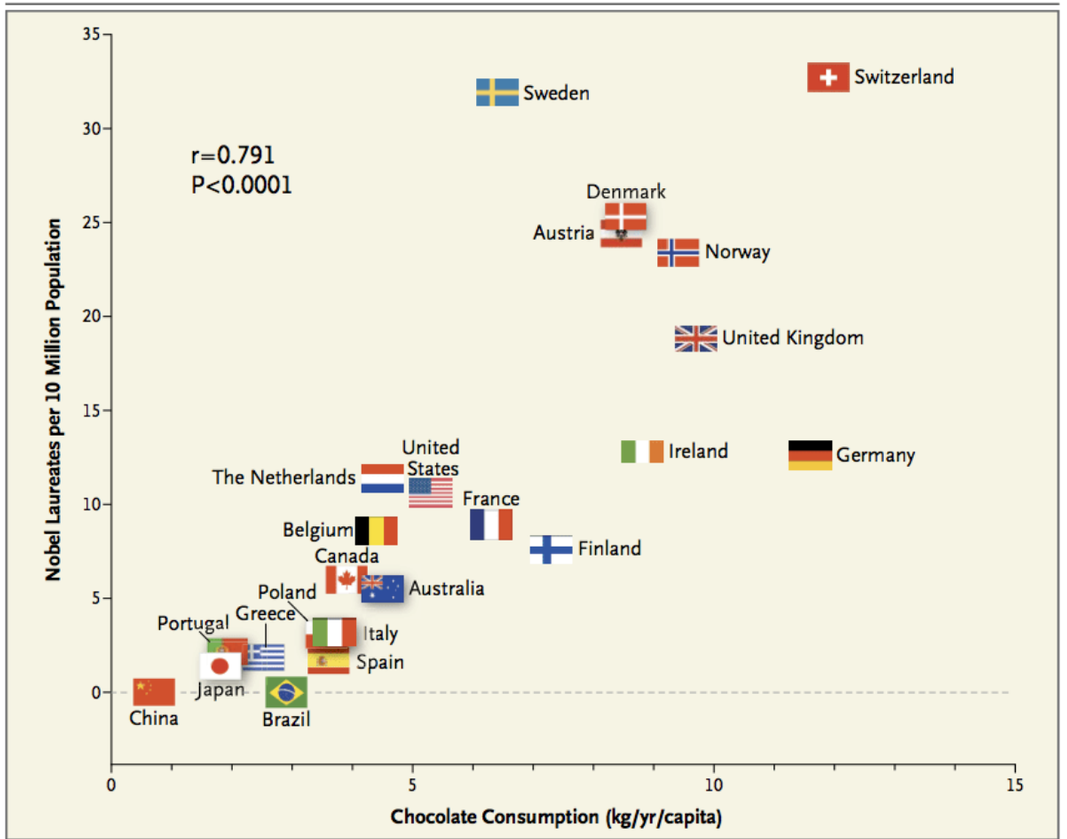

Figure 1. Correlation between Countries’ Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Introduction

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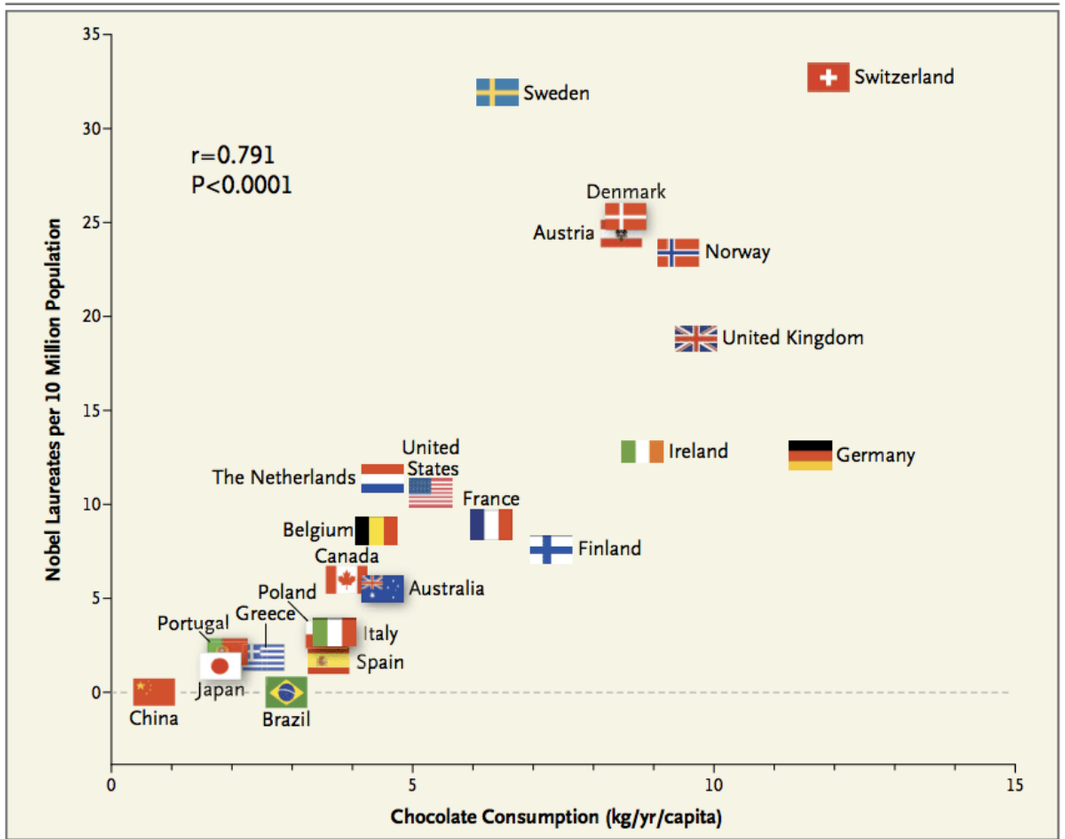
This would imply: “countries with more chocolate consumption tent to have more Nobel laureates”

But NOT necessarily imply “the more chocolate I consume, the more likely I am to win the Nobel Prize”



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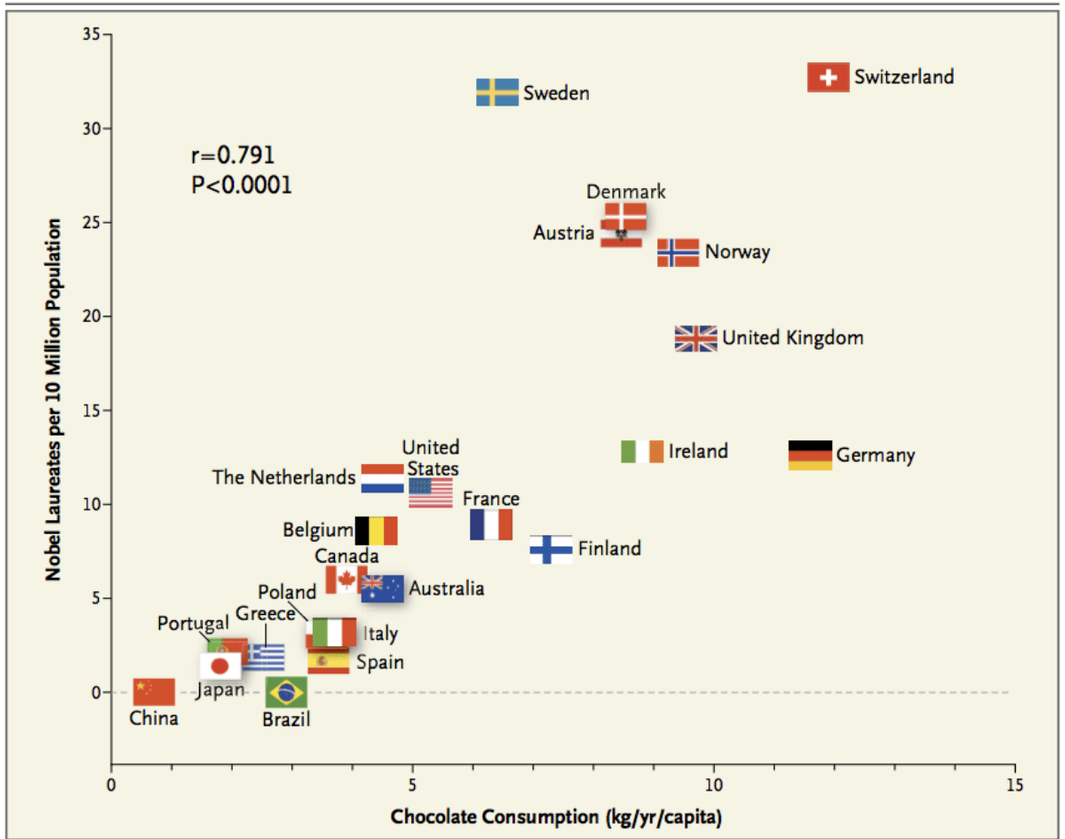
Cannot get causation from observational data only



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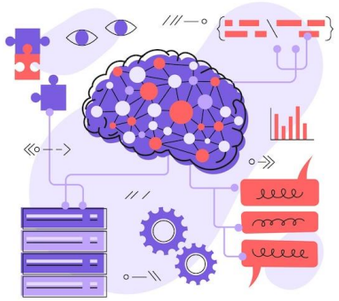
Introduction

Why should I automate ML protocols?

- **Algorithmic innovation**



- **Data availability**

- **Computer power**

Introduction

Why should I automate ML protocols?

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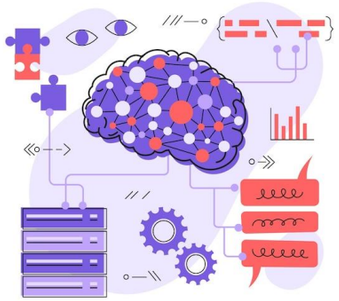
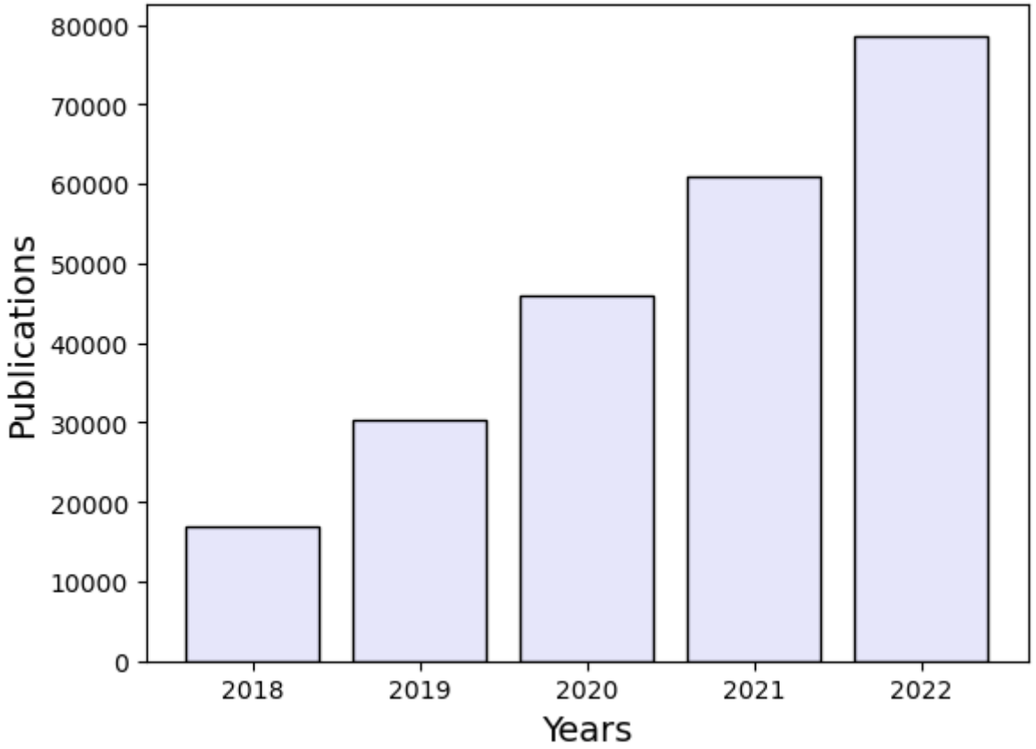


- **Data availability**

- **Computer power**

"Machine Learning" search in Reaxys



Year 2022: 78622 publications (≈ 215 /day)

Introduction

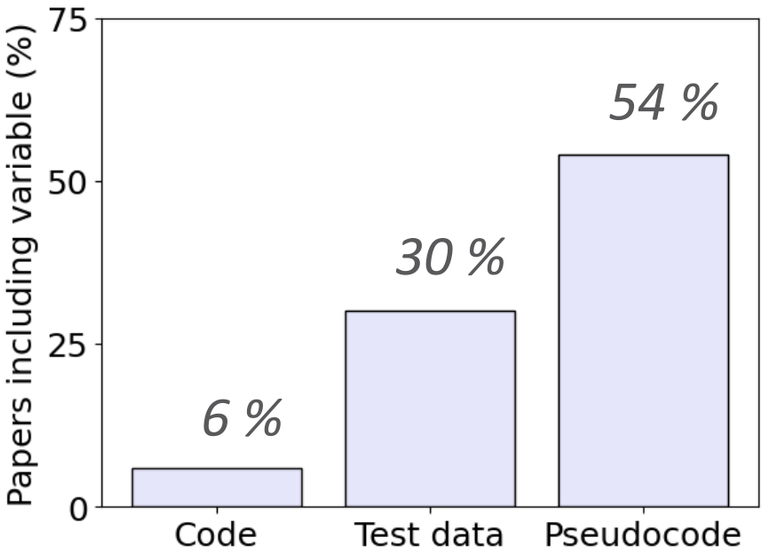
Why should I automate ML protocols?

"The growth of machine learning and making it FAIR"

Nat. Chem. ***13****, 505–508 (2021).*

"Artificial intelligence faces reproducibility crisis"

Science **359**,725-726(2018).



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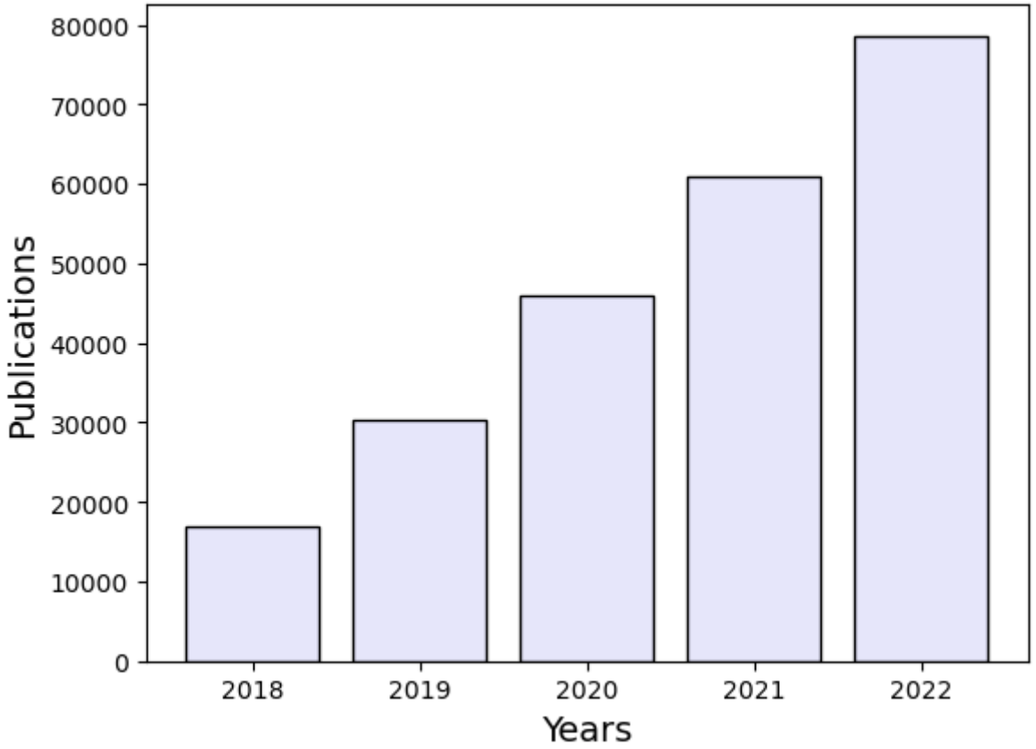

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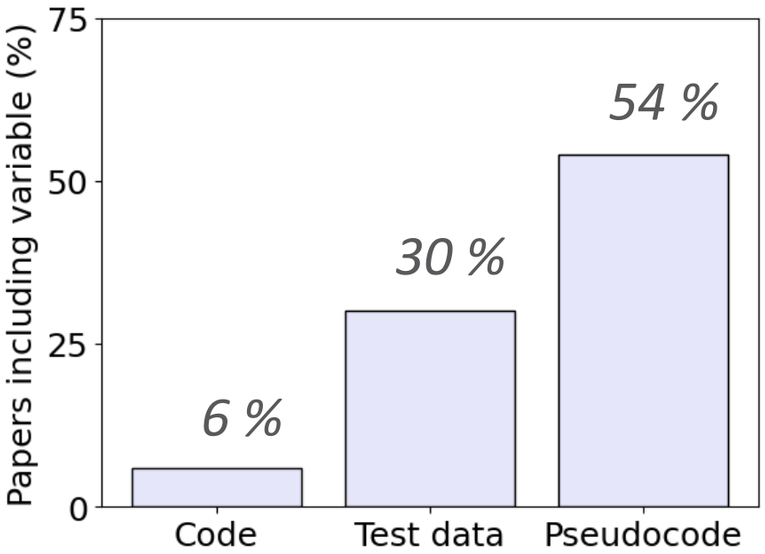

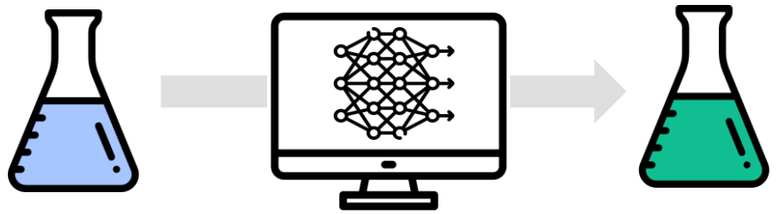

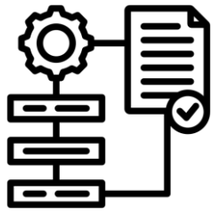

Protocols

Standards

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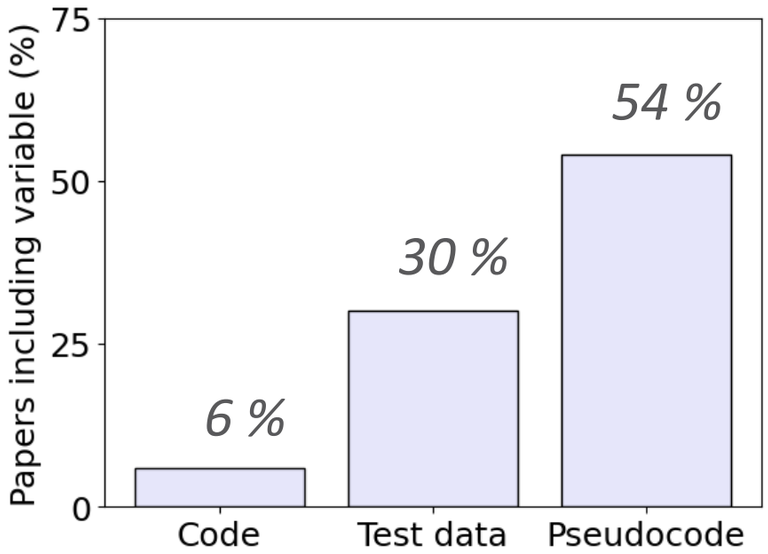

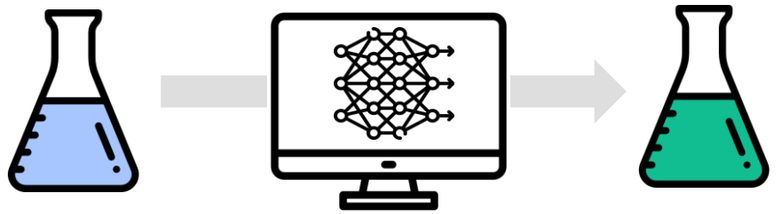

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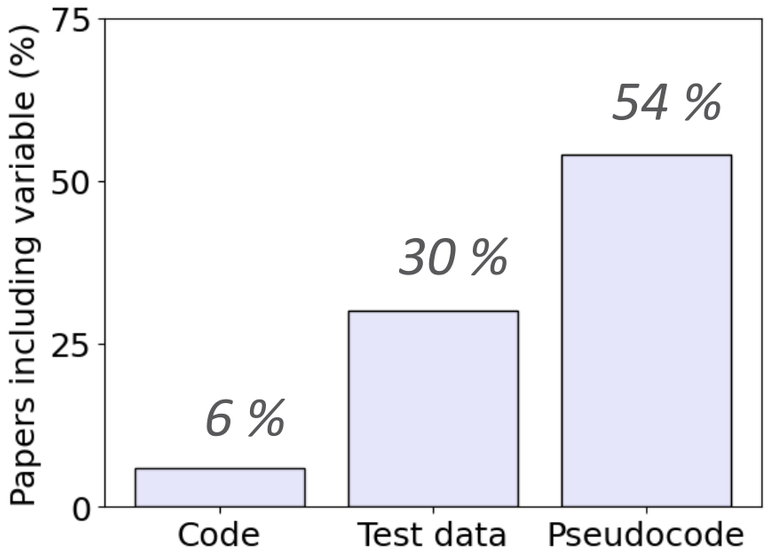
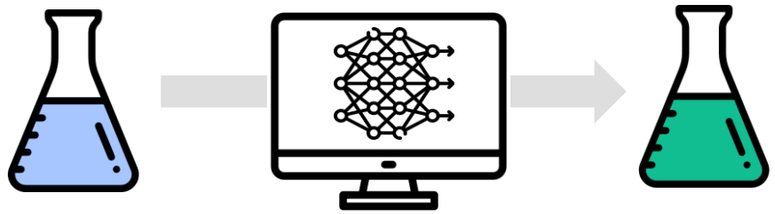
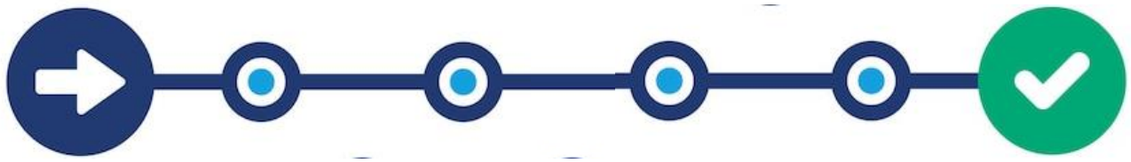




Protocols

Standards



Introduction

R²OBERT AUTOMATED ML PROTOCOLS

THE Alegre GROUP

R²OBERT

Most chemists: inexperienced ML users

ML experts

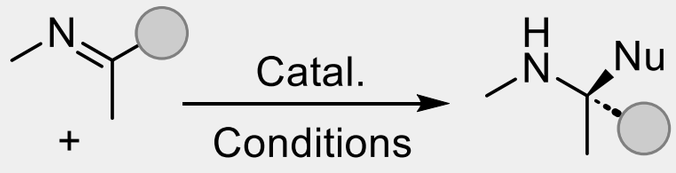
user-specific workflows

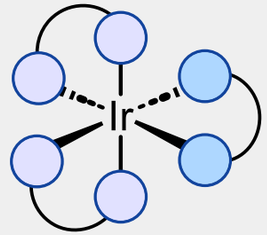
Automated

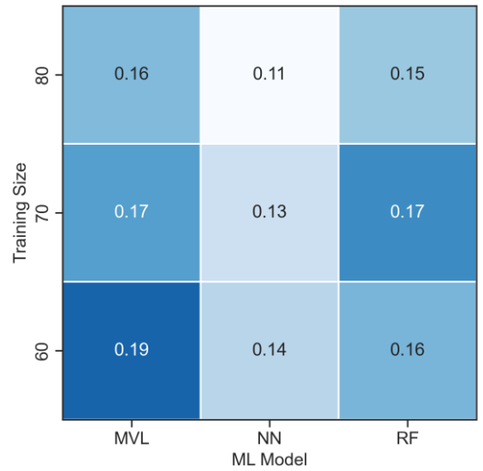
1 Data curation

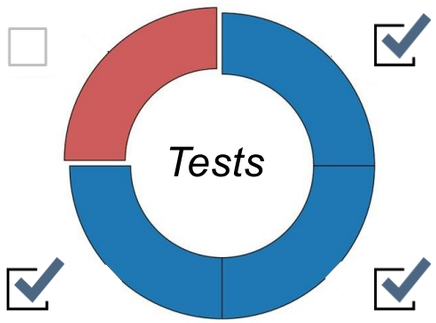
2 Model optimization

Common chemical ML problems







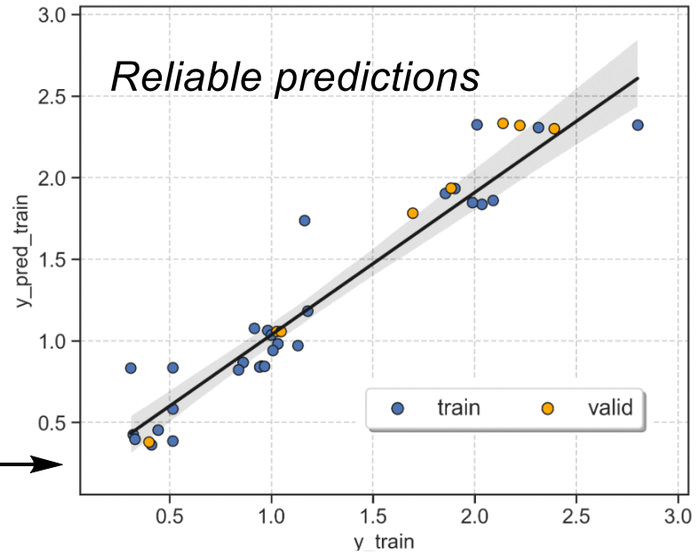


Verification

3

Predictor

4



Introduction

	Proton Number	First	Second	Third	Fourth
H	1	1310	–	–	–
He	2	2370	5250	–	–
Li	3	519	7300	11800	–
Be	4	900	1760	14800	21000
B	5	799	2420	3660	25000
C	6	1090	2350	4610	6220
N	7	1400	2860	4590	7480
O	8	1310	3390	5320	7450
F	9	1680	3370	6040	8410
Ne	10	2080	3950	6150	9290
Na	11	494	4560	6940	9540
Mg	12	736	1450	7740	10500
Al	13	577	1820	2740	11600
Si	14	786	1580	3230	4360
P	15	1060	1900	2920	4960
S	16	1000	2260	3390	4540
Cl	17	1260	2300	3850	5150
Ar	18	1520	2660	3950	5770
K	19	418	3070	4600	5860
Ca	20	590	1150	4940	6480
Sc	21	632	1240	2390	7110
Ti	22	661	1310	2720	4170
V	23	648	1370	2870	4600
Cr	24	653	1590	2990	4770
Mn	25	716	1510	3250	5190
Fe	26	762	1560	2960	5400
Co	27	757	1640	3230	5100
Ni	28	736	1750	3390	5400
Cu	29	745	1960	3350	5690

Database

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- Support Vector Machine
- Decision Tree
- Ensemble Trees
- Generalized Additive Model
- Neural Network
- Linear Regression
- Gaussian Process Regression

Database

ML model selection

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Database

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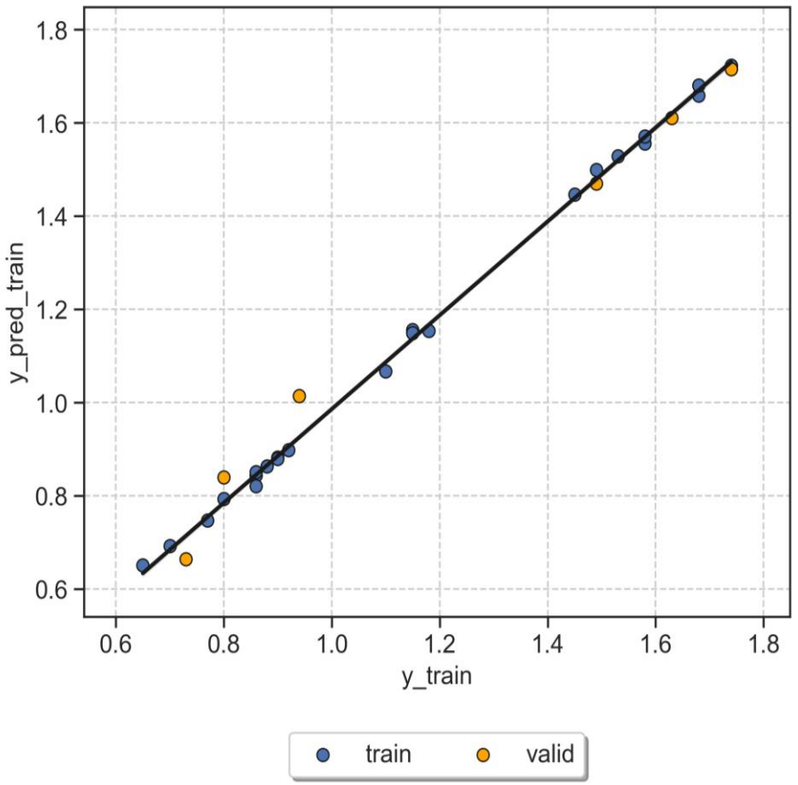
ML model selection



Results

Introduction

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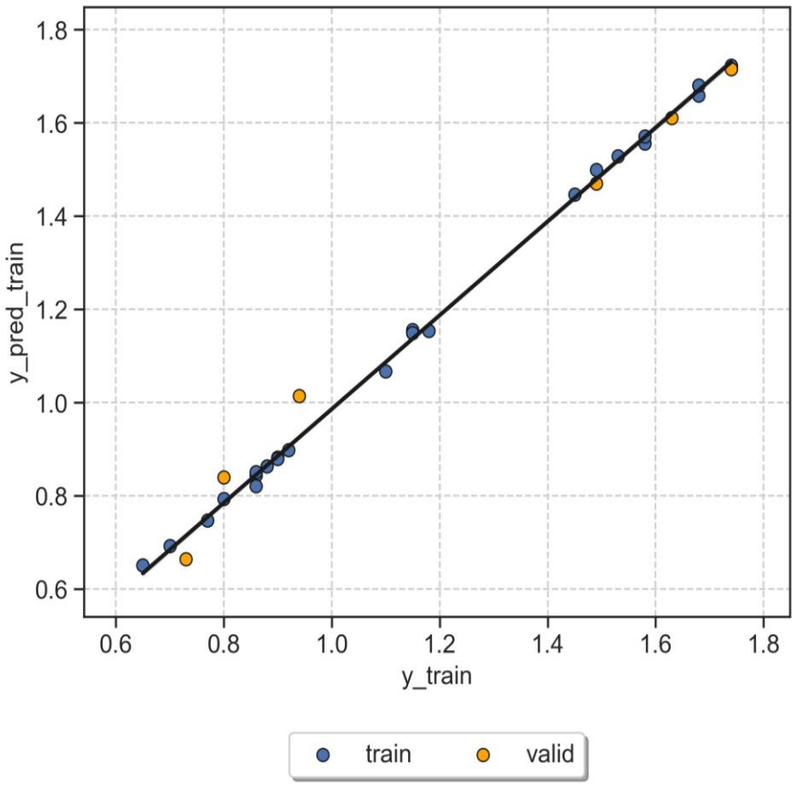

Database **ML model selection** **Results**

1 command line

Installation

Installation (instructions in Read the Docs)

- **Windows, macOS and Linux:**

1. Download Anaconda

2. Open a terminal with Anaconda

3. Copy/paste commands from Read the Docs

Quick note for users with no Python experience

You need a terminal with Python to install and run ROBERT. These are some suggested first steps:

For Windows users:

1. Install Anaconda with Python 3.
2. Open an Anaconda prompt.
3. Create a conda environment called "robert" with Python (`conda create -n robert python=3.10`).
   You only need to do this once.
4. Activate the conda environment called "robert" (`conda activate robert`).
5. Install ROBERT as defined in the "Installation" section (`conda install -c conda-forge robert`).
6. Go to the folder with your CSV database (using the "cd" command, i.e. `cd C:/Users/test_robert`).
7. Run ROBERT as explained in the Examples section.

https://robert.readthedocs.io

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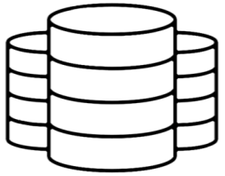
- **Nine testers with varying Python level:** *between 30 s - 2 min*

** No Python experience at all: install Anaconda +5 min*

https://robert.readthedocs.io

ROBERT: automation of ML protocols



- *CSV database*

Input: CSV file with database or SMILES

User-defined descriptors

X_i — y

code_name	charge	LUMO	...	solub.
mol_5	0	-6,581	...	-13,3
mol_13	0	-5,375	...	-2,68
mol_16	0	-4,349	...	-1,41
mol_34	0	-6,557	...	-1,64

or

Automated: SMILES to descriptors

y

SMILES	solub.
c1ccsc1	-13,3
CCCC=C	-2,68
CC(C)Cl	-1,41
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X_i

- Charge
- FOD
- Chi_n
- V_{bur}

...

200+ descriptors

(RDKit, xTB & DBSTEP)

Executing ROBERT: only one command line needed

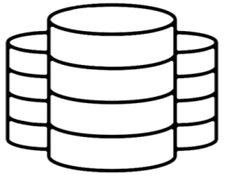
python -m robert --csv_name FILENAME.csv --y y_NAME (--ARG1 --ARG2 ...)

① Data curation ② Model optimization ③ Verification ④ Predictor

- ☑ *Data curation*
- ☑ *ML model scan*
- ☑ *Statistical tests*
- ☑ *Predictor model*
- ☑ *Outlier analysis*
- ☑ *AQME tandem*

Full workflow in one command line

ROBERT: automation of ML protocols



- *CSV database*

ROBERT
AUTOMATED ML PROTOCOLS

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ROBERT: automation of ML protocols

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R²OBERT
AUTOMATED ML PROTOCOLS

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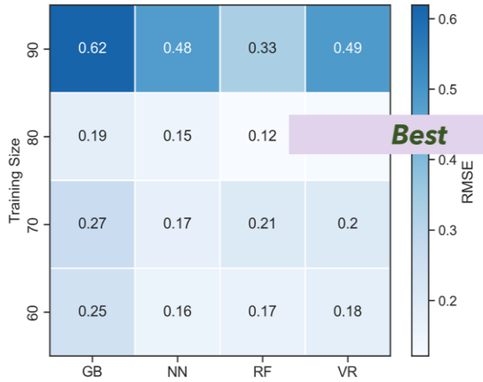
Full workflow in one command line

CURATE

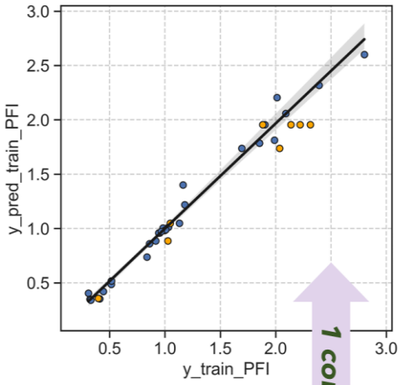
Data curation process

- *Discard noise*
- *Discard correlated descriptors*
- *Categorical data conversion*
- *Duplicate filter*

GENERATE



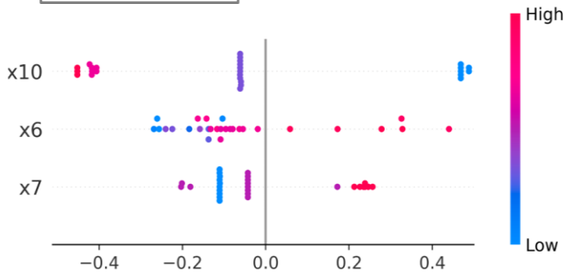
Best



- *ML model and partition screening*
- *PFI filtering*

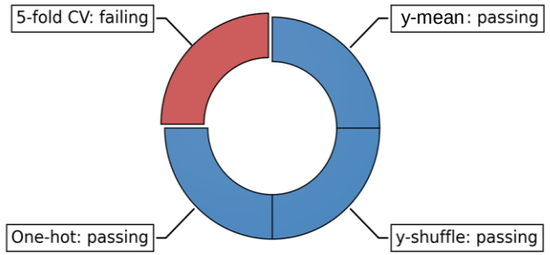
1 command line

PREDICT



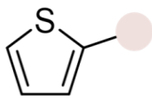
- *External test set*
- *SHAP Analysis*

VERIFY

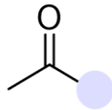


- *Statistical test analysis*

AQME



C1=CC=CS1
ClC1=CC=CS1



CC(C)=O
CC(C(C)NC)=O

- *SMILES to results*

ROBERT: automation of ML protocols

CURATE

1. Filters off **correlated descriptors**

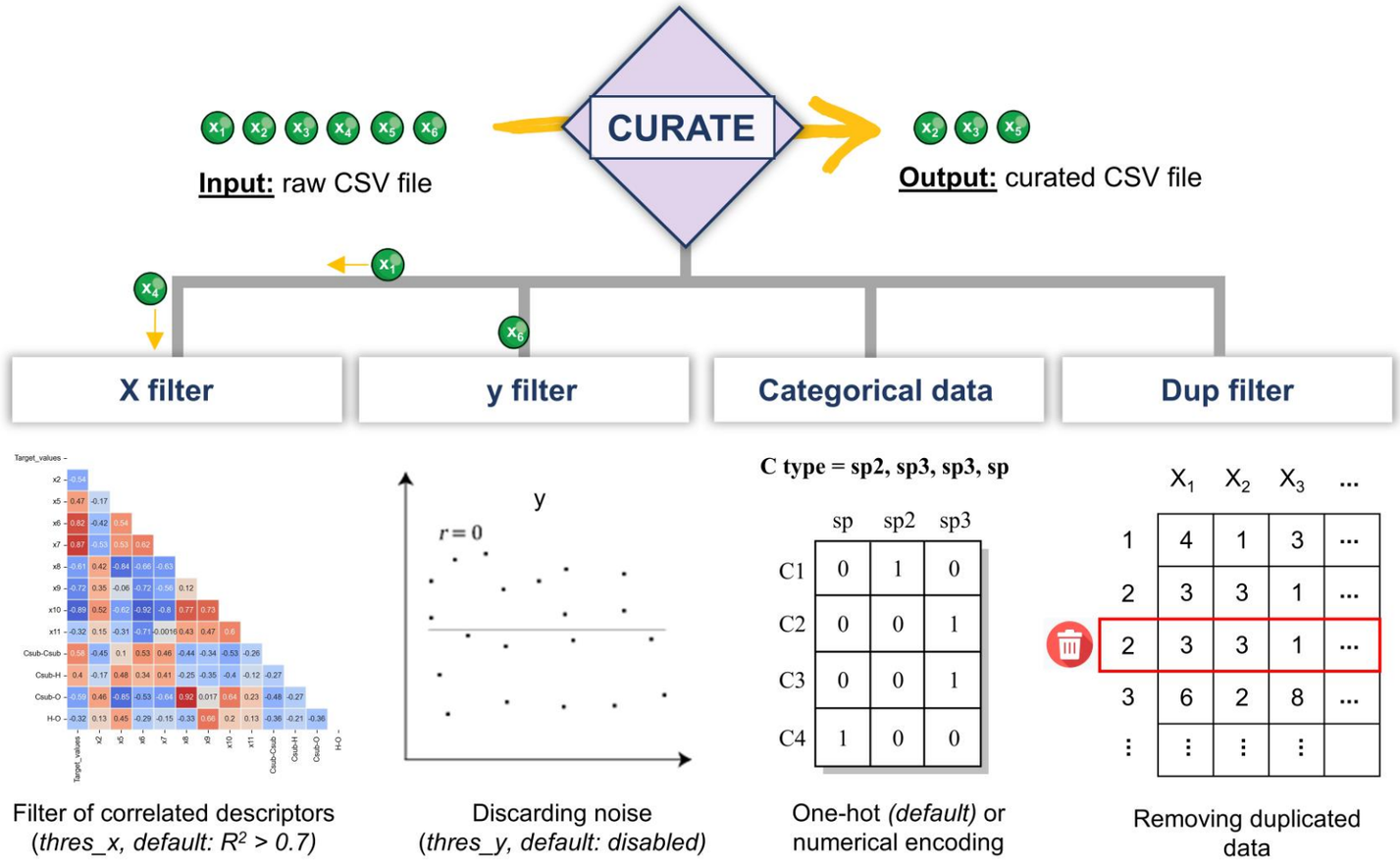
2. Filters off variables with very low correlation to the target values (**noise**)

3. Converts **categorical descriptors** into one-hot descriptors

4. Filters off **duplicates**

5. Filters off **missing values**
(KNN imputer, if >30% discard descriptor)

6. Keeping the **descriptors to 1/3 of the datapoints** (RFECV)



ROBERT: automation of ML protocols

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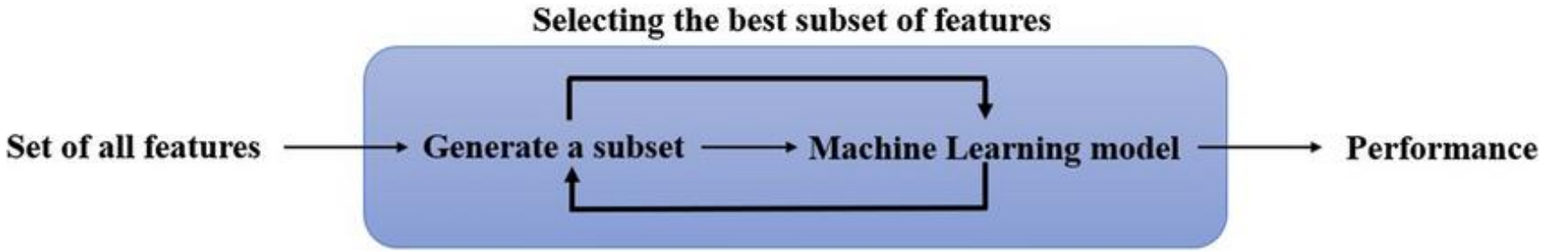
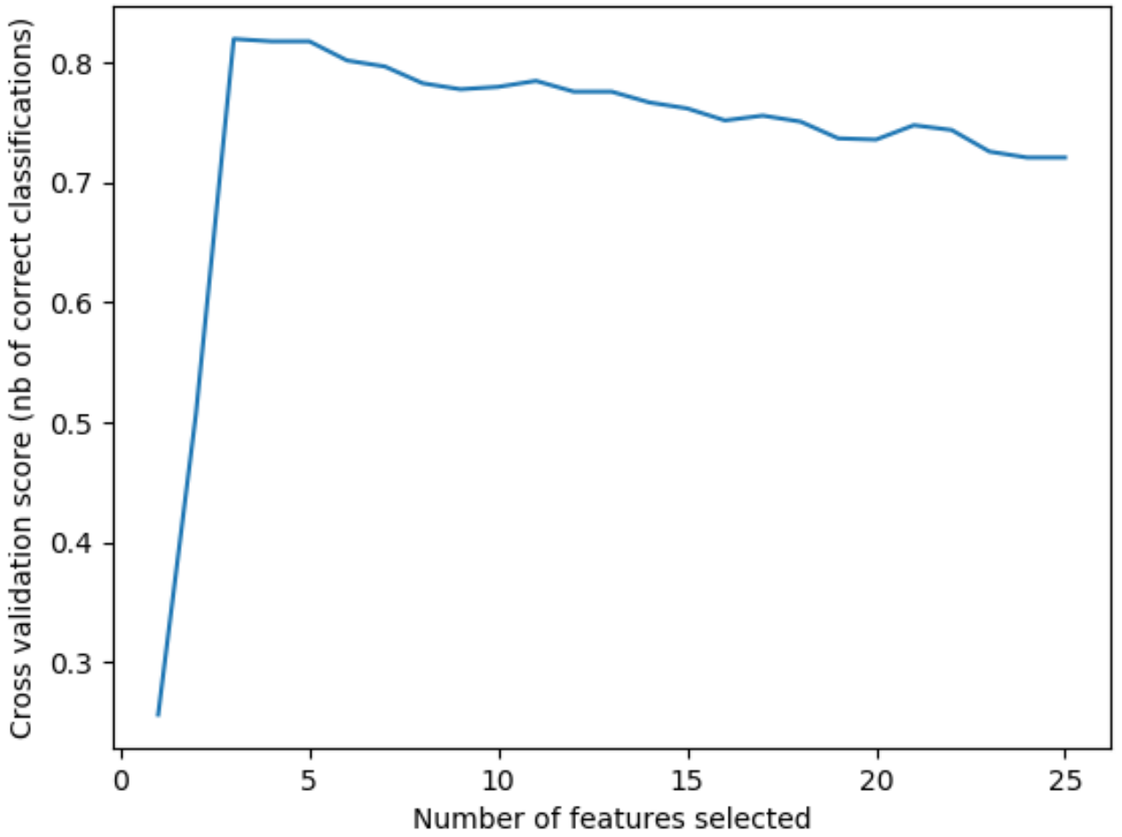




ROBERT: automation of ML protocols

GENERATE

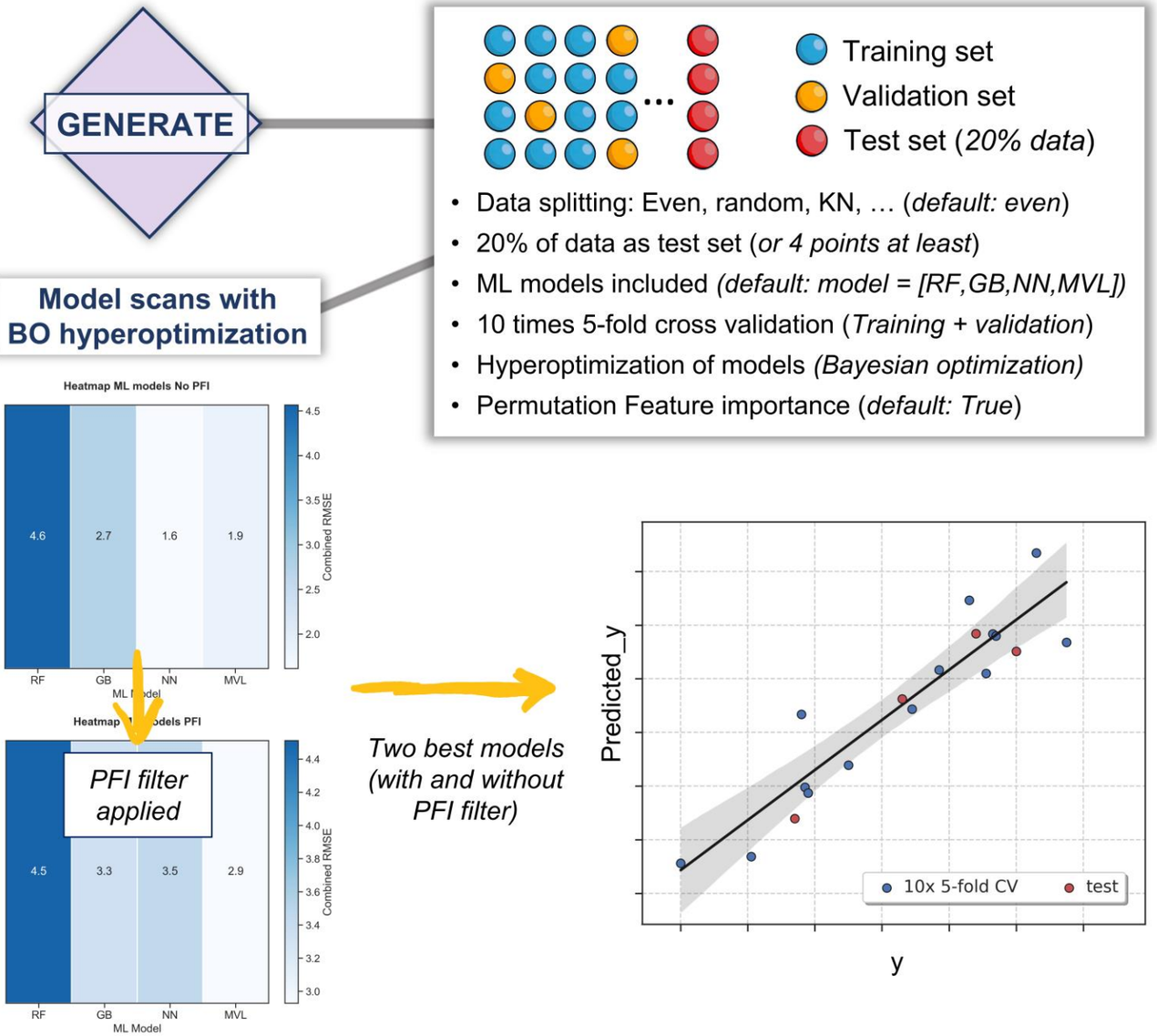
1. **Data Splitting (**Train / Validation Test)

2. **Hyperoptimizes** multiple ML models (Bayesian Optimization)

3. Filters off descriptors with low permutance feature importance (**PFI**).

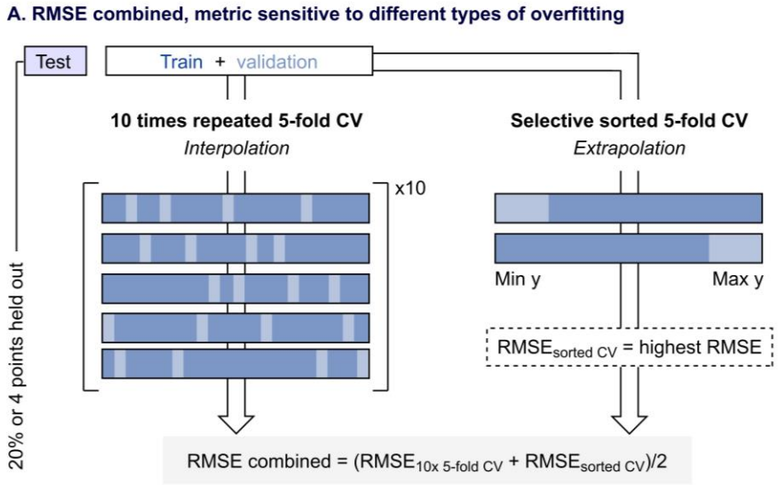
4. Creates a **heatmap plot** with different model types and partition sizes.

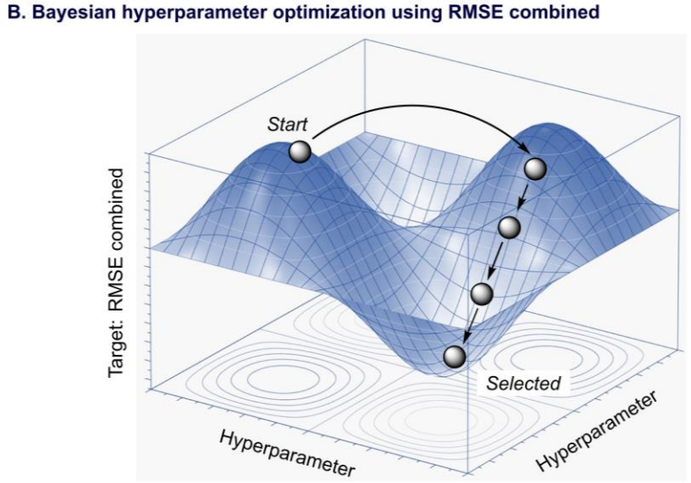
5. Selects and stores the **best** No PFI and PFI **models**

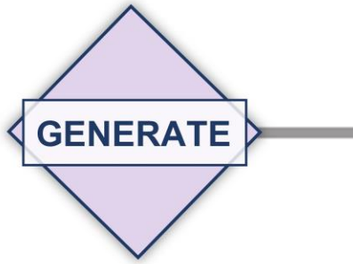


ROBERT: automation of ML protocols

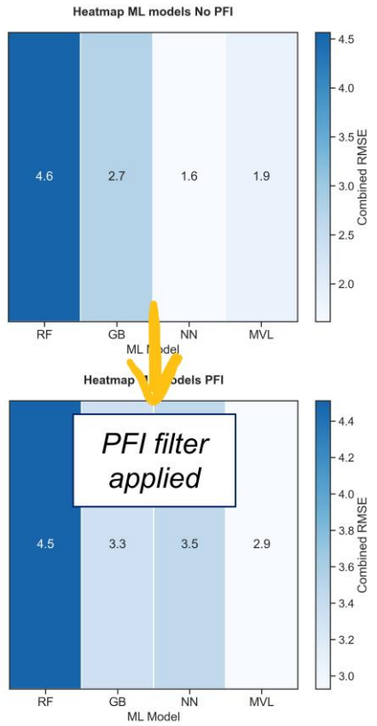
GENERATE

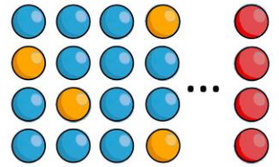






Model scans with BO hyperoptimization

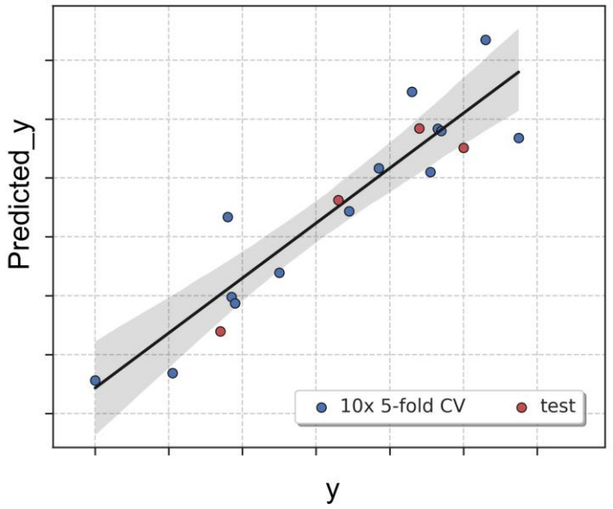




- Training set
- Validation set
- Test set (*20% data*)

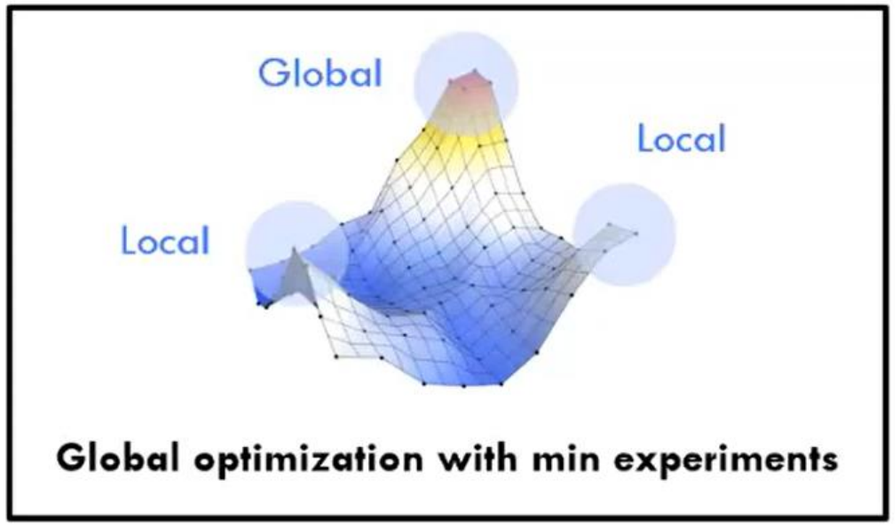
- Data splitting: Even, random, KN, … (*default: even*)
- 20% of data as test set (*or 4 points at least*)
- ML models included *(default: model = [RF,GB,NN,MVL])*
- 10 times 5-fold cross validation (*Training + validation*)
- Hyperoptimization of models *(Bayesian optimization)*
- Permutation Feature importance (*default: True*)

Two best models (with and without PFI filter)



ROBERT: automation of ML protocols

BO

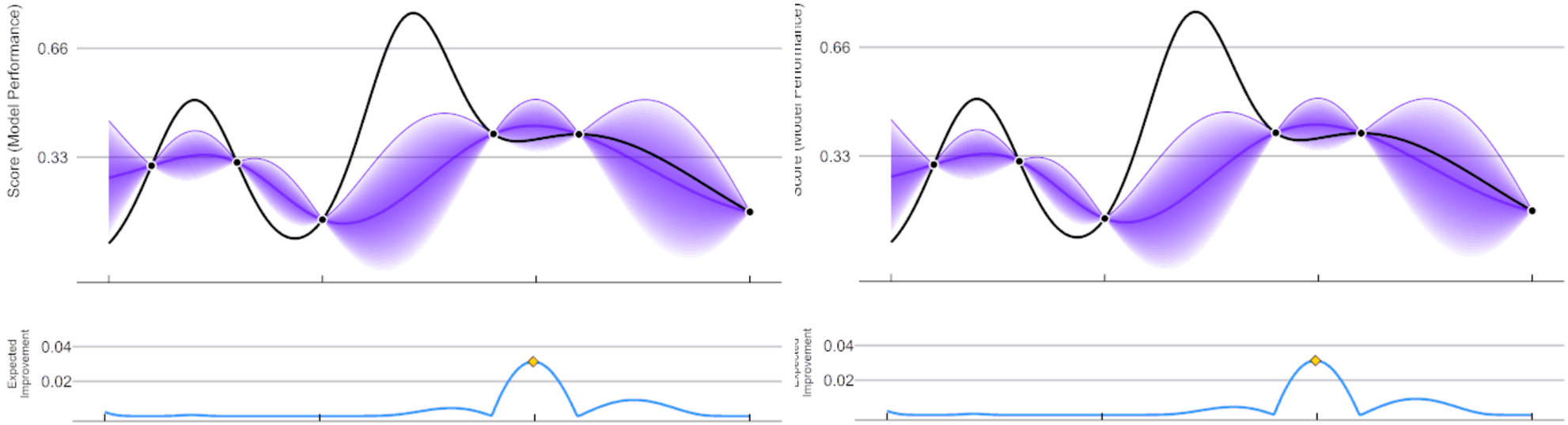


$$EI(x) = \begin{cases} (\mu(x) - f^{+} - \delta)\Phi + \sigma(x)\varphi \\ 0 \end{cases}$$

SD

$\uparrow SD \rightarrow \uparrow$ *Expected Improvement*

Statistical uncertainty drives optimization



https://github.com/doyle-lab-ucla/edboplus

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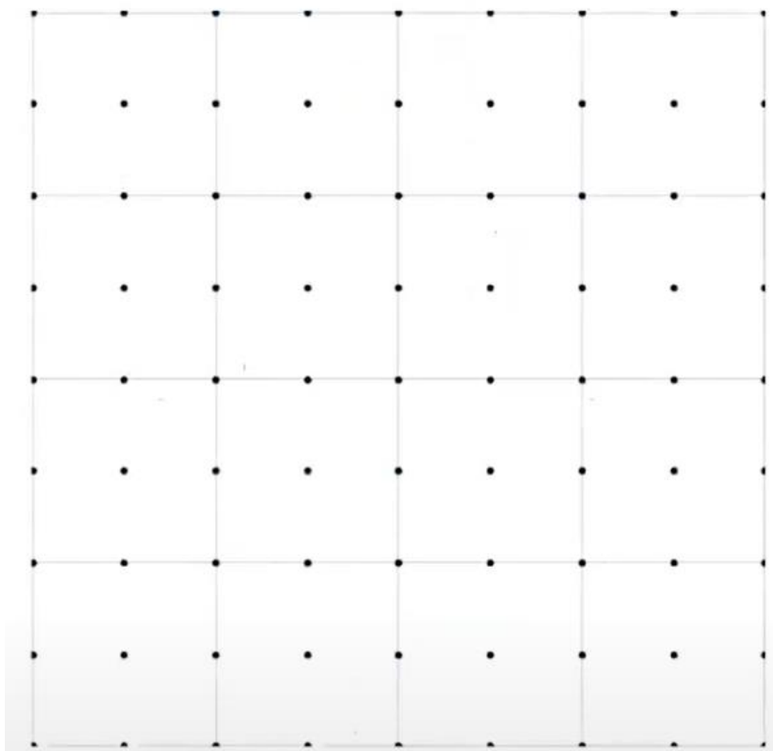
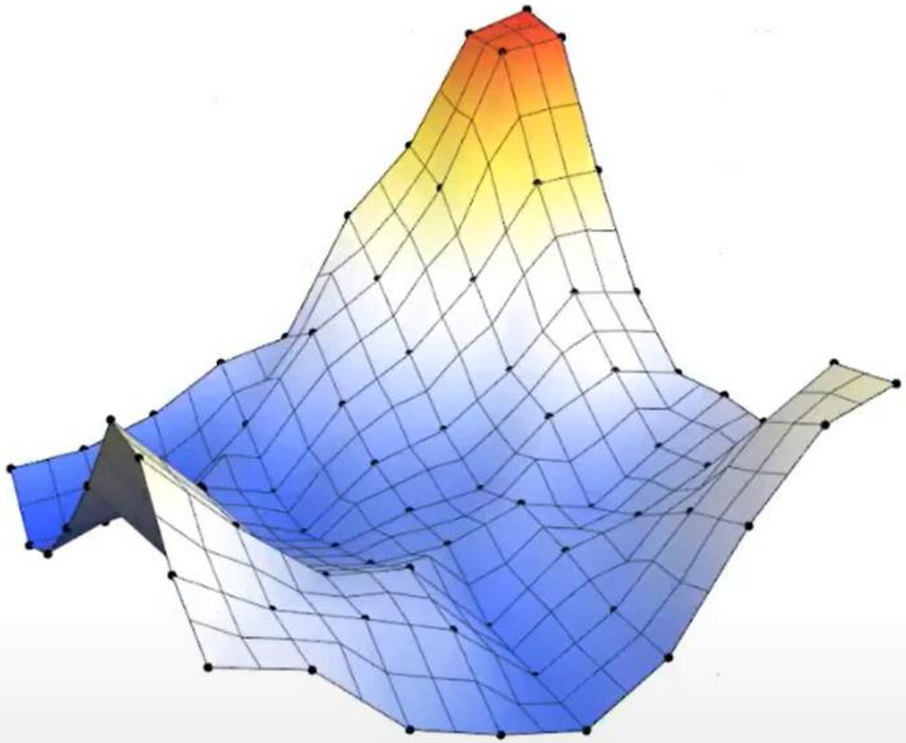
BO

Search space



RMSE combined



RMSE combined space

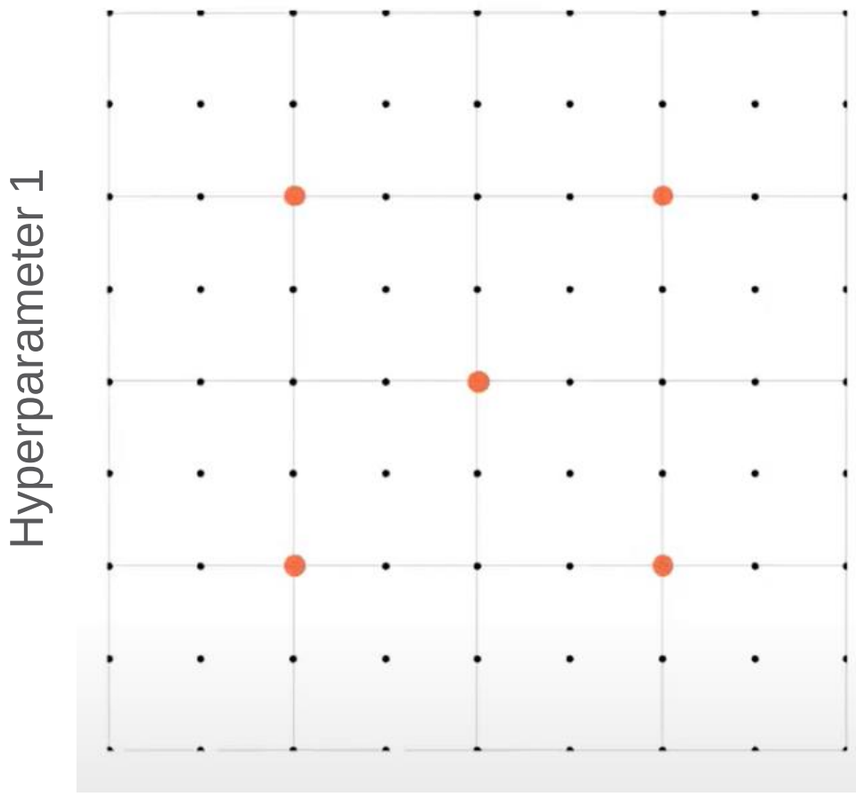
We start by defining a search space over which we seek to minimize the RMSE combined metric

https://github.com/doyle-lab-ucla/edboplus

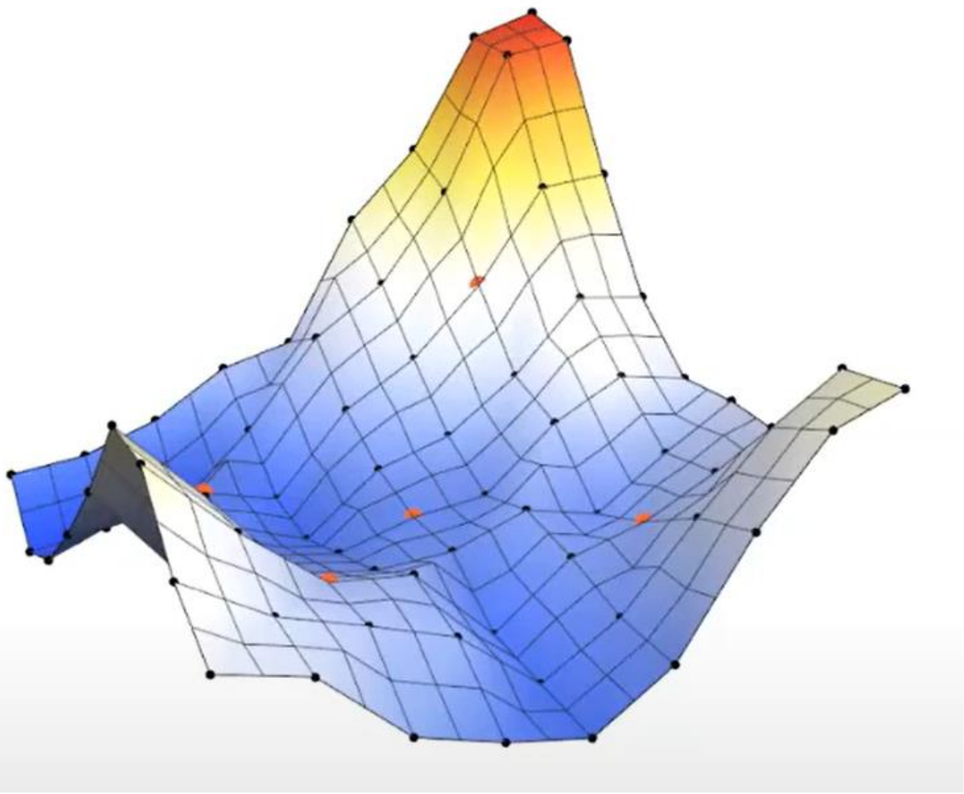
ROBERT: automation of ML protocols

BO

Search space



RMSE combined



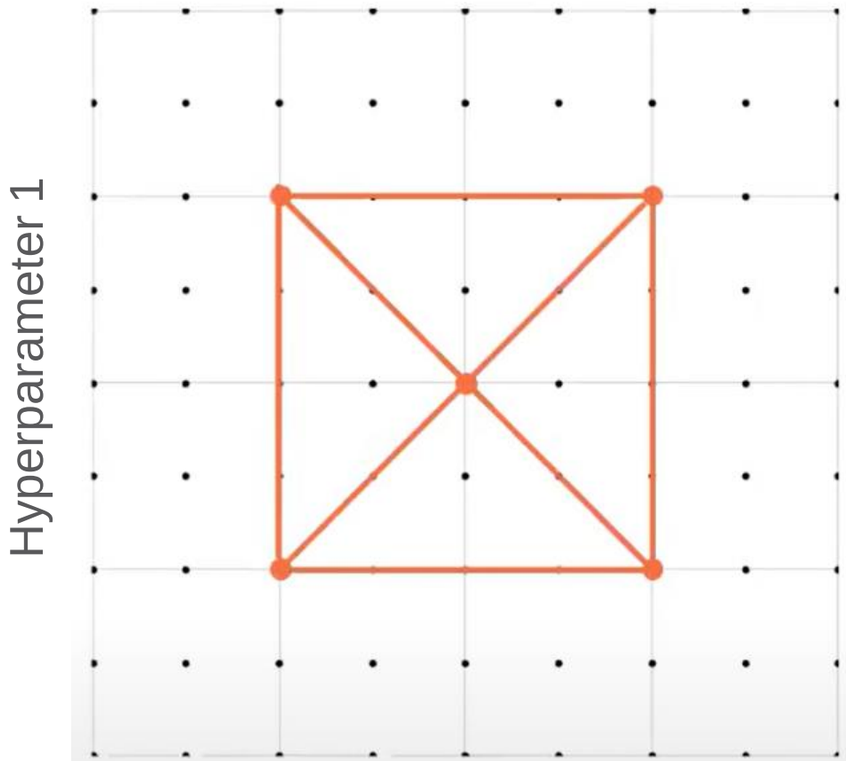
The optimizer is initialized by collecting RMSE combined using some random initial hyperparameters

https://github.com/doyle-lab-ucla/edboplus

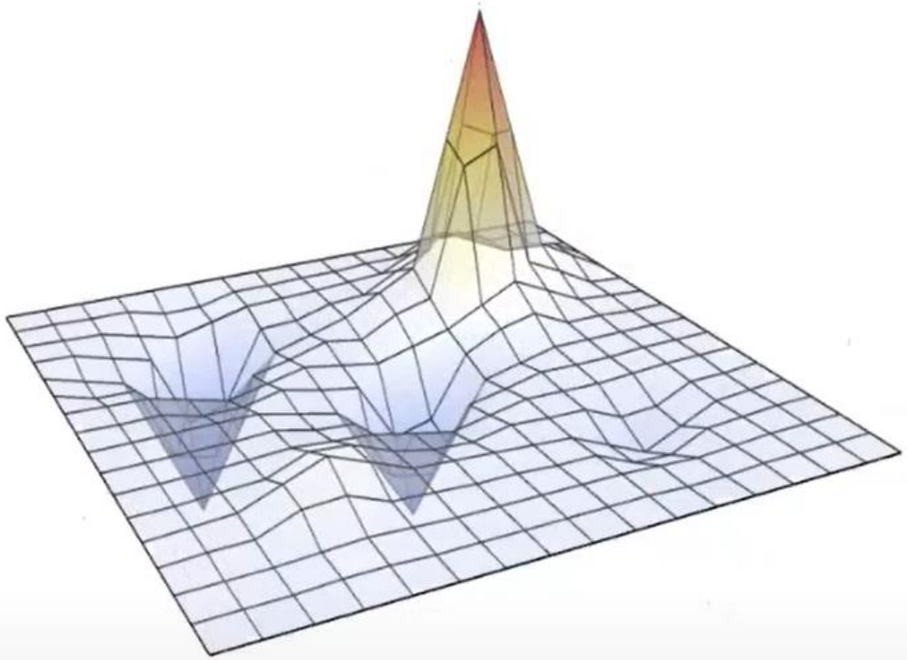
ROBERT: automation of ML protocols

BO

Search space



Surrogate model



Gaussian Process

A model is then fit to the data – key model requirements are predictions and estimates of variance

https://github.com/doyle-lab-ucla/edboplus

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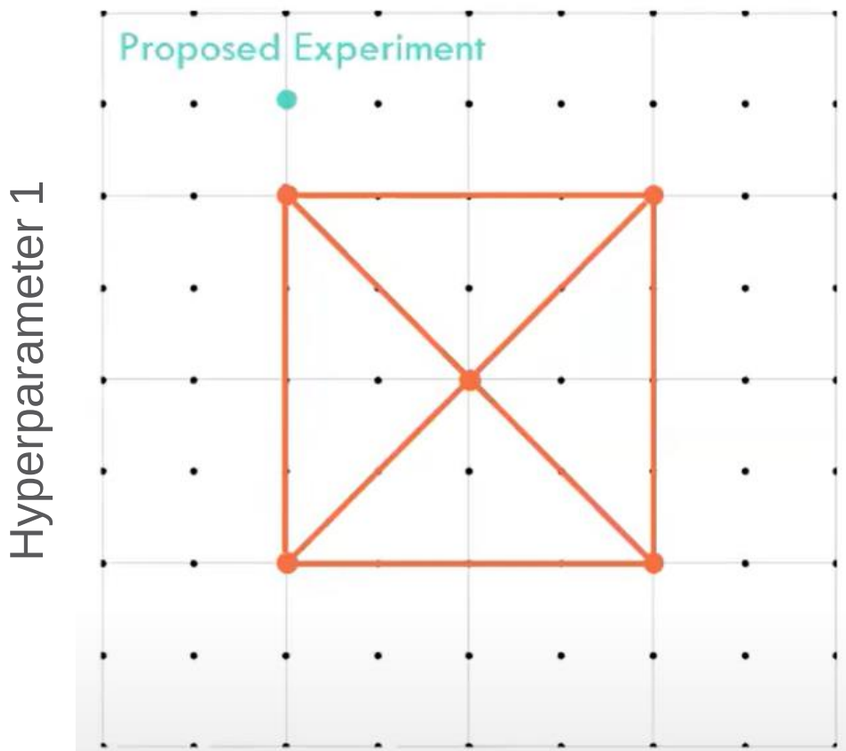
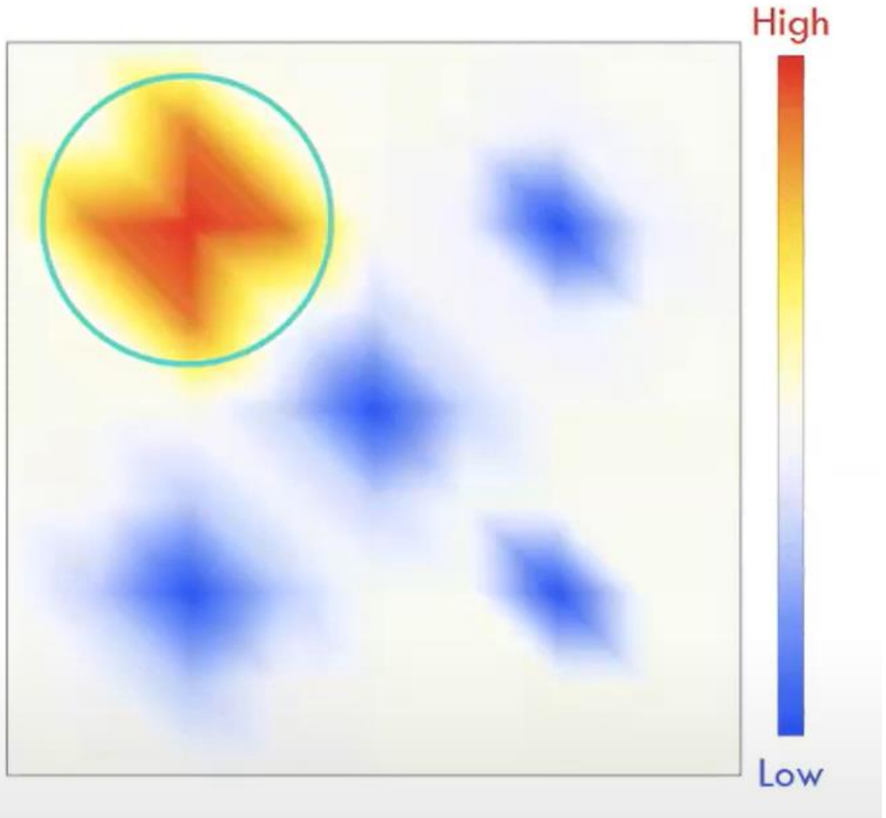
BO

Search space



Acquisition function

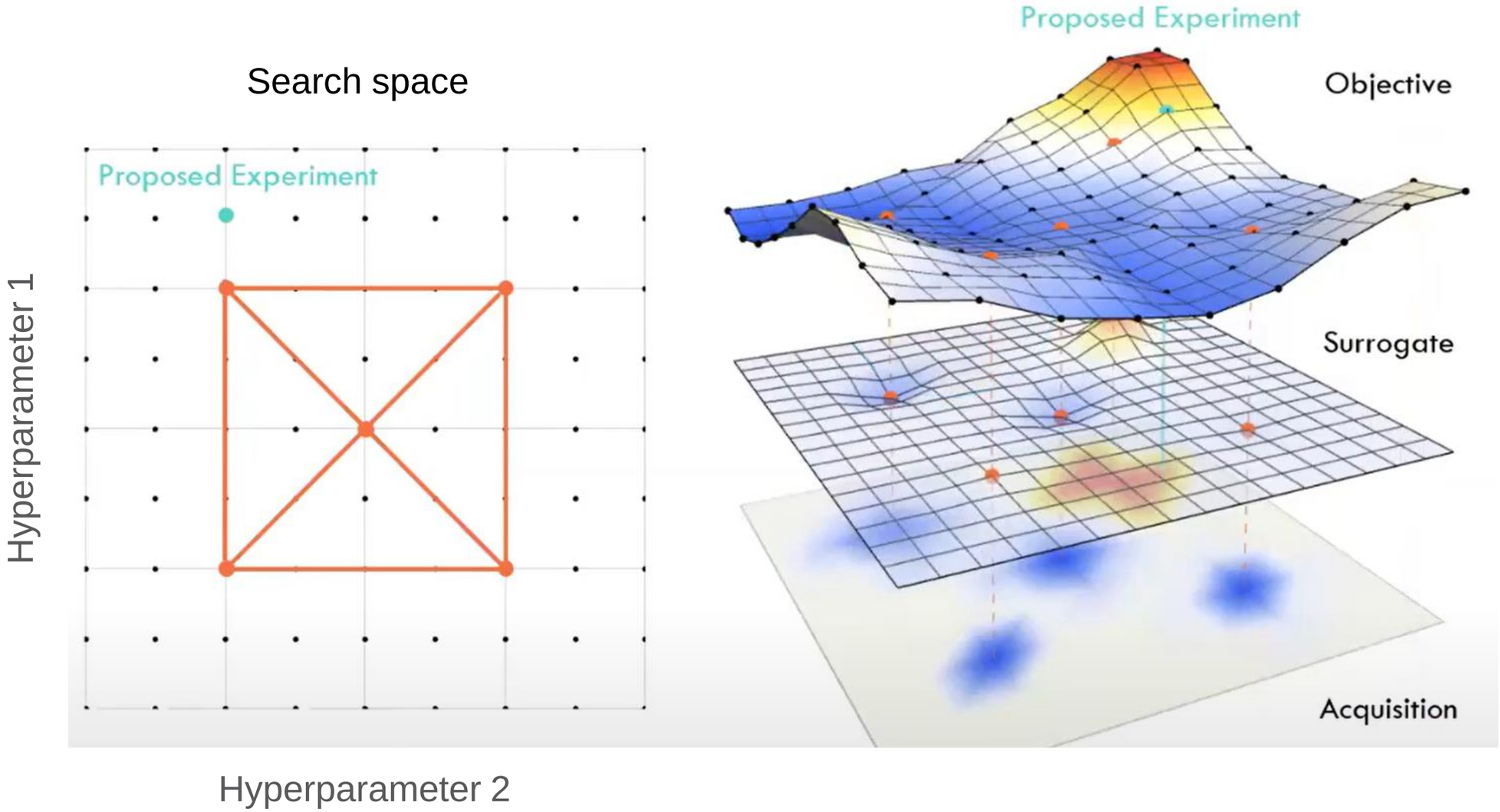


An acquisition function is derived from the surrogate model to select the next hyperparameters

https://github.com/doyle-lab-ucla/edboplus

ROBERT: automation of ML protocols

BO

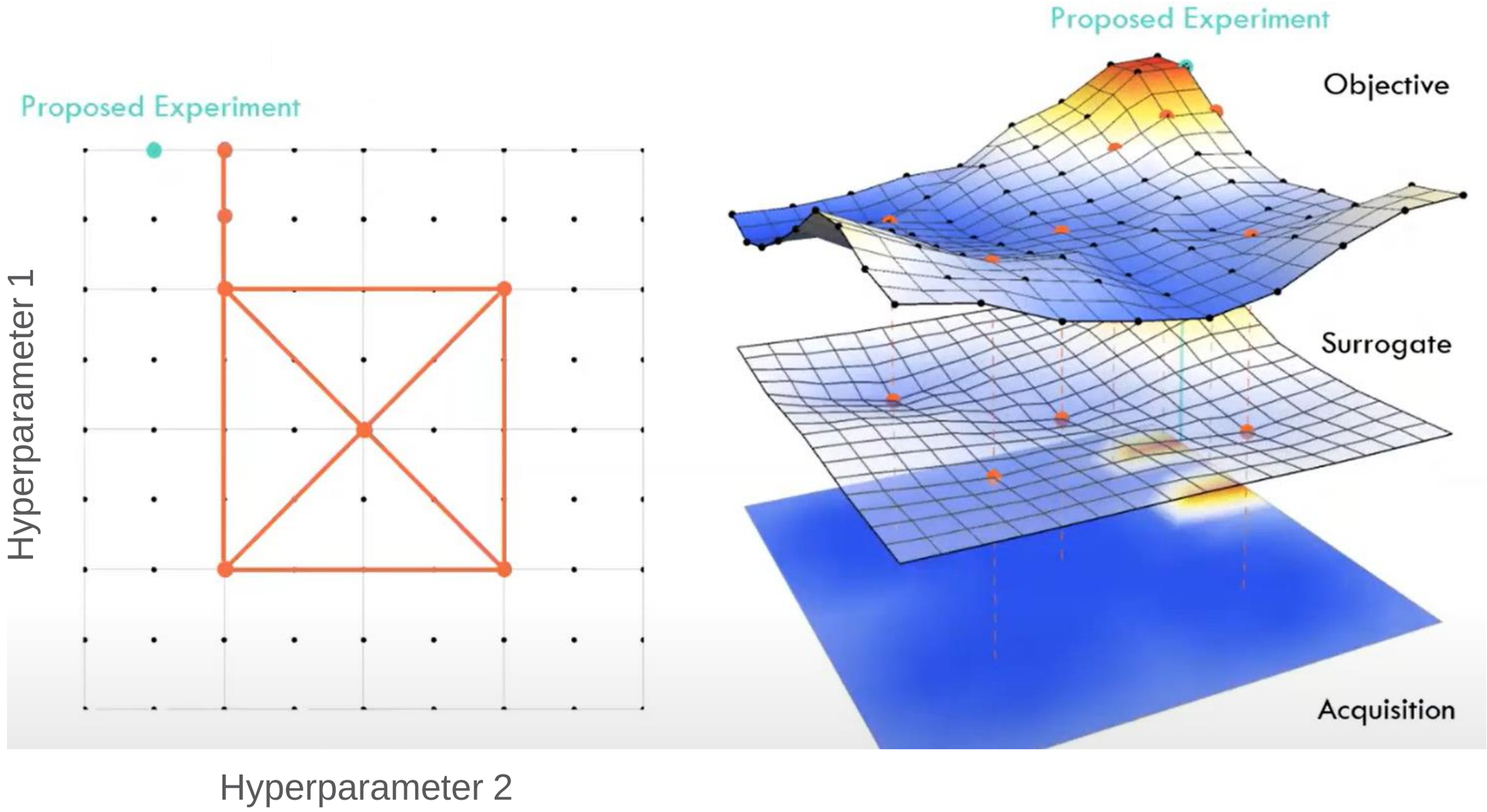


This process is iterated until optimization is complete or resources are depleted

https://github.com/doyle-lab-ucla/edboplus

ROBERT: automation of ML protocols

BO



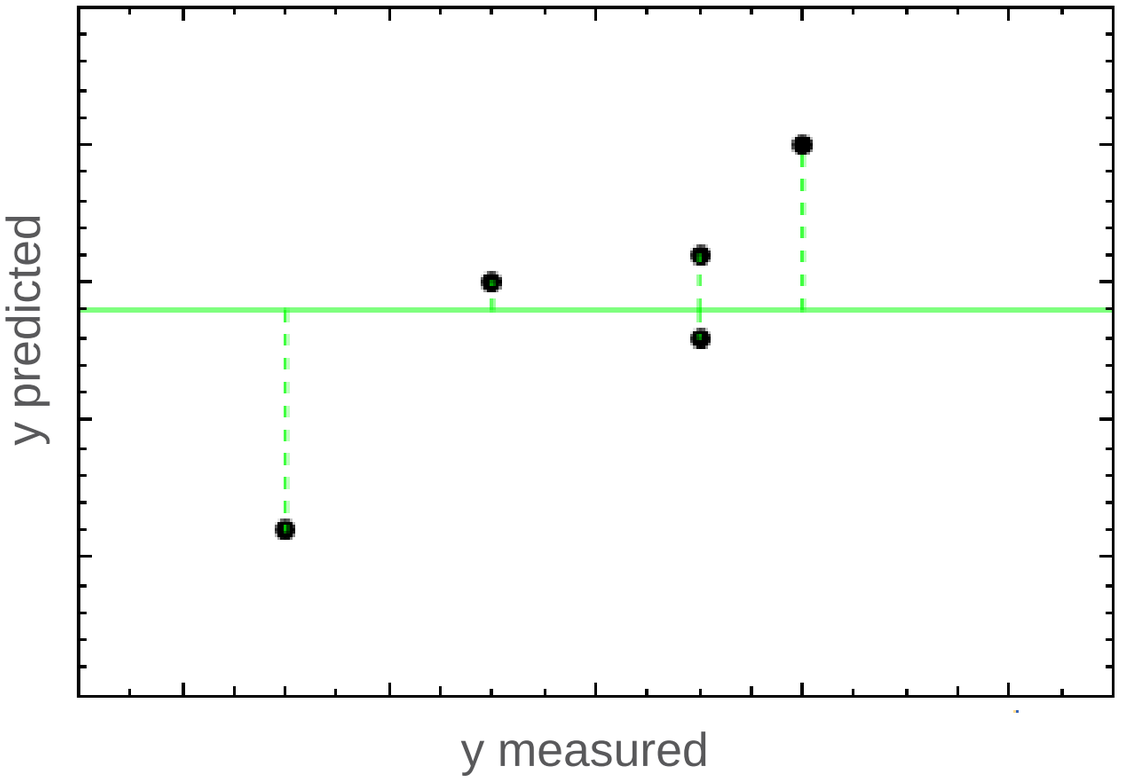
This process is iterated until optimization is complete or resources are depleted

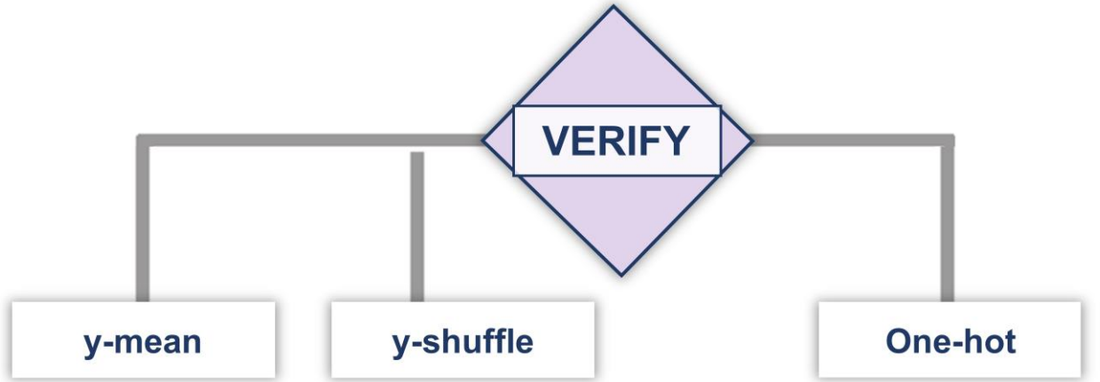
https://github.com/doyle-lab-ucla/edboplus

ROBERT: automation of ML protocols

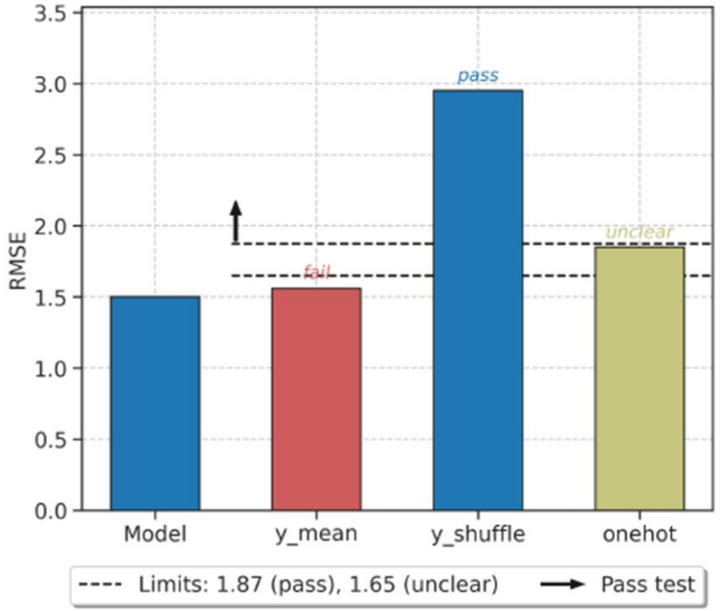
VERIFY

1. **y-mean test**: Calculates the accuracy of the model when all the predicted y values are fixed to the mean of the y values





- Error using only the mean y value
- Shuffles y values
- Replaces X values for 0s and 1s



Color codes:
- Blue: passing test
- Yellow: unclear result
- Red: failing test

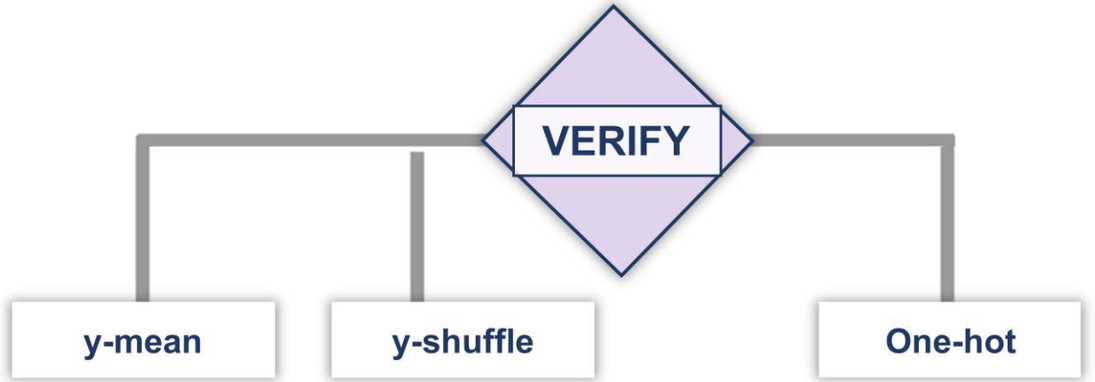
Threshold defaults:
Passing = 30 % of model
Unclear = 15 % of model

ROBERT: automation of ML protocols

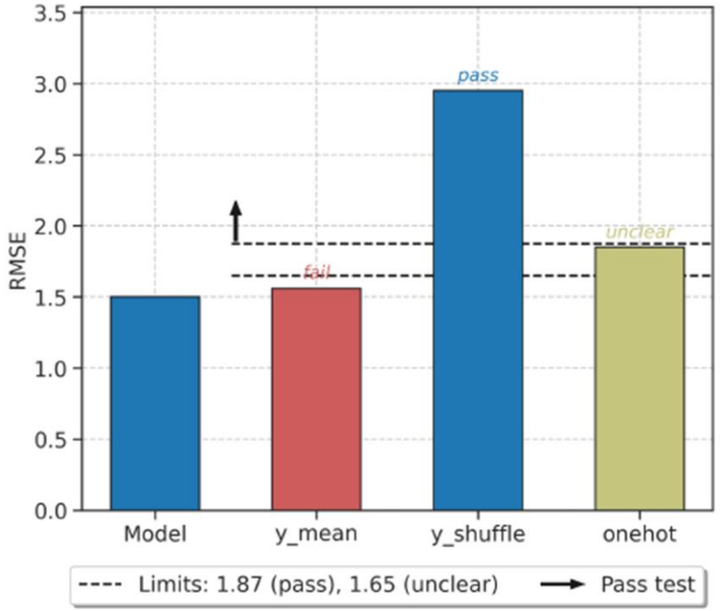
VERIFY

2. **y-shuffle test**: Calculates the accuracy of the model after shuffling randomly all the measured y values

Name	X1	y	y-shuffle
A	4,1	15	22
B	5,3	10	5
C	-2,4	5	10
D	15,1	15	2
E	-7,8	22	15
F	-0,2	2	15



- Error using only the mean y value
- Shuffles y values
- Replaces X values for 0s and 1s



Color codes:
- Blue: passing test
- Yellow: unclear result
- Red: failing test

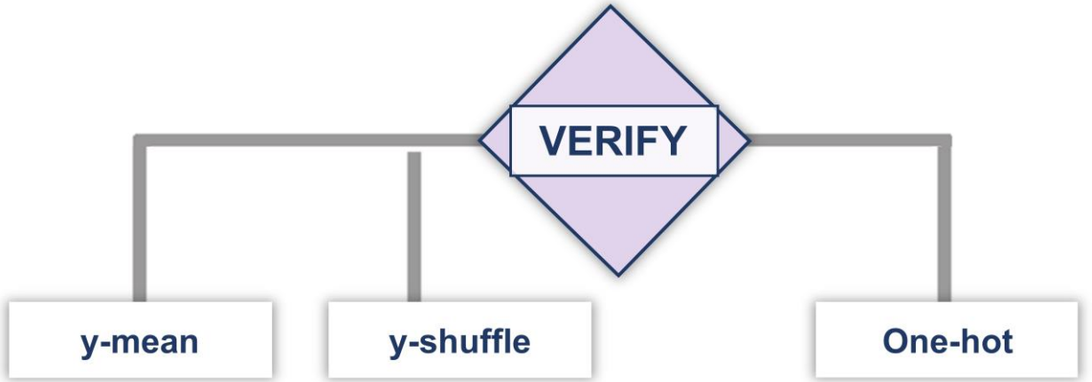
Threshold defaults:
Passing = 30 % of model
Unclear = 15 % of model

ROBERT: automation of ML protocols

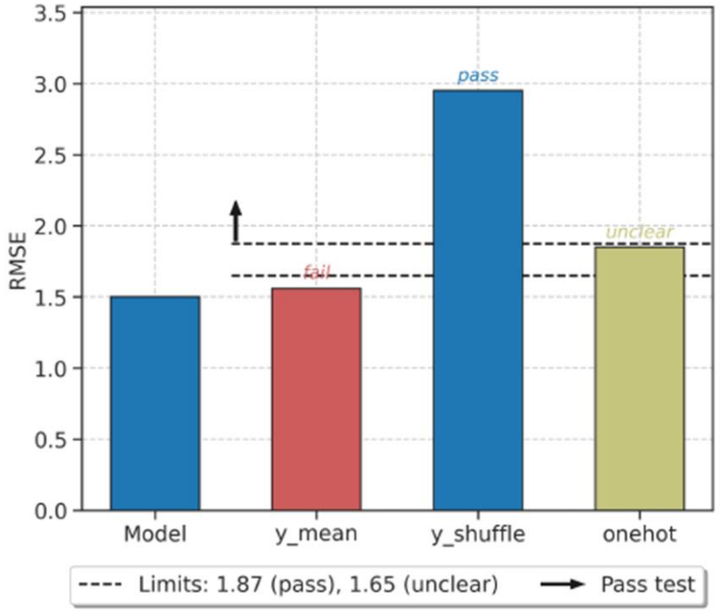
VERIFY

3. **One-hot test**: Calculates the accuracy of the model when replacing all descriptors for 0s and 1s

Name	X1	X1-OH	y
A	4,1 →	1	15
B	5,3 →	1	10
C	0,0 →	0	5
D	15,1 →	1	15
E	0,0 →	0	22
F	0,0 →	0	2



- Error using only the mean y value
- Shuffles y values
- Replaces X values for 0s and 1s



Color codes:
- Blue: passing test
- Yellow: unclear result
- Red: failing test

Threshold defaults:
Passing = 30 % of model
Unclear = 15 % of model

ROBERT: automation of ML protocols

PREDICT

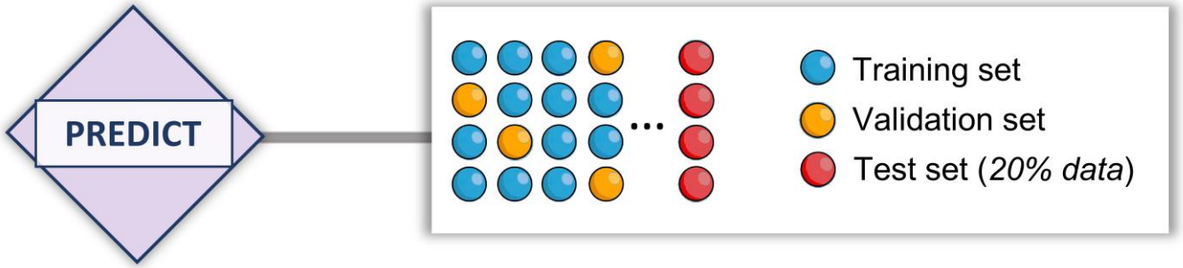
1. Calculates **R2**, **MAE** and **RMSE** (for regression) or **accuracy**, **F1** score and **MCC** (for classification)

2. Predicts values for an **external test set** (if any)

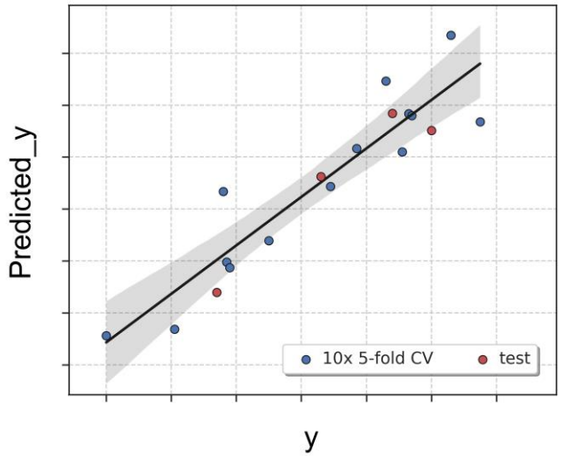
3.Performs an **outlier analysis**

4. Performs a **SHAP** feature **analysis**

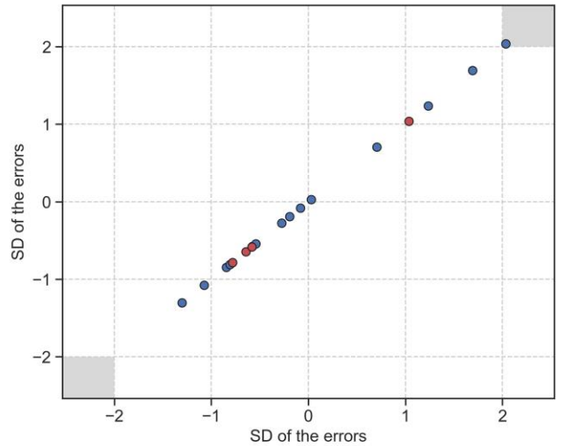
5. Performs a **PFI** feature **analysis**



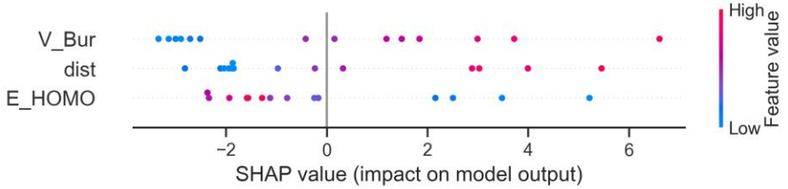
- 10x 5-fold CV (Training + validation) + test data



- Outlier analysis (*default: t_value = 2*)



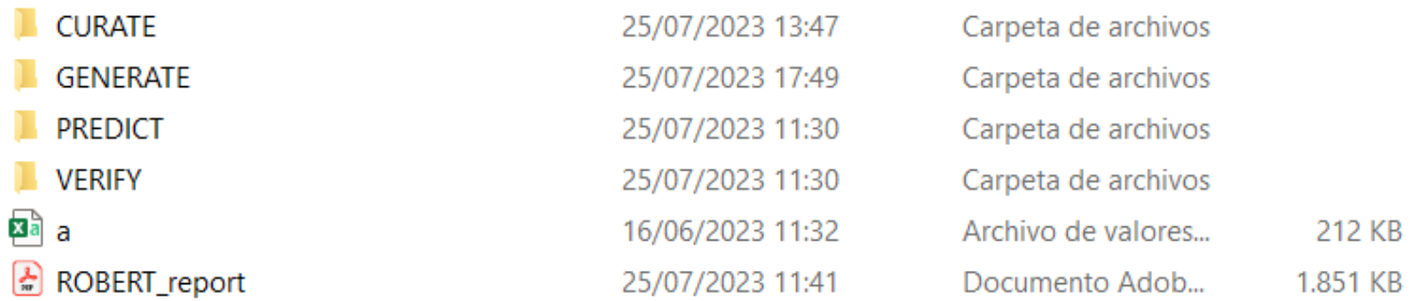
- SHAP and PFI analysis



ROBERT: automation of ML protocols

Results

- A series of folders with the names of the modules used will be created in the folder where ROBERT was executed.



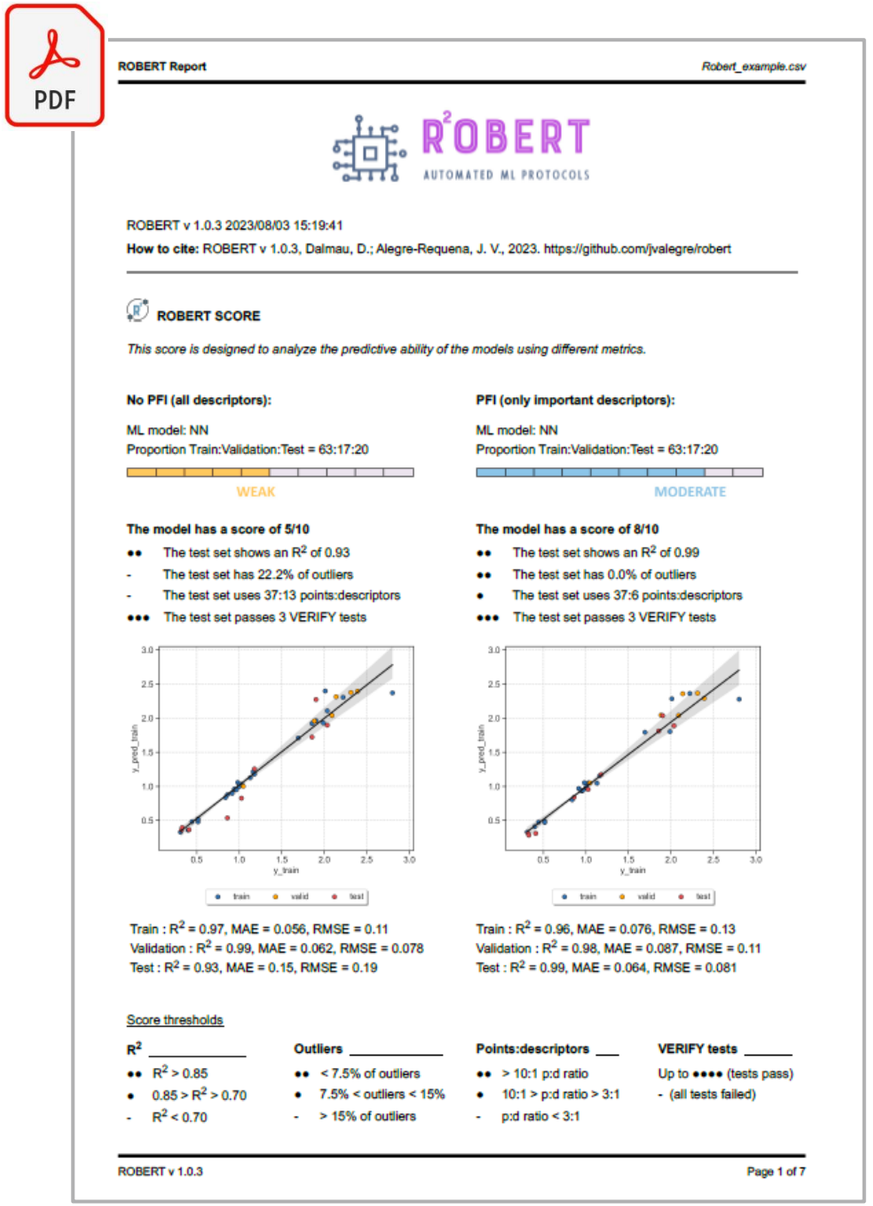
ROBERT: automation of ML protocols

Results

- A series of folders with the names of the modules used will be created in the folder where ROBERT was executed.

CURATE	25/07/2023 13:47	Carpeta de archivos	
GENERATE	25/07/2023 17:49	Carpeta de archivos	
PREDICT	25/07/2023 11:30	Carpeta de archivos	
VERIFY	25/07/2023 11:30	Carpeta de archivos	
a	16/06/2023 11:32	Archivo de valores...	212 KB
ROBERT_report	25/07/2023 11:41	Documento Adob...	1.851 KB

- A PDF file called **ROBERT_report.pdf** will be created with the most important information



PDF

ROBERT Report — Robert_example.csv

ROBERT v 1.0.3 2023/08/03 15:19:41

How to cite: ROBERT v 1.0.3, Dalmau, D.; Alegre-Requena, J. V., 2023. https://github.com/jvalegre/robert

ROBERT SCORE

This score is designed to analyze the predictive ability of the models using different metrics.

No PFI (all descriptors):

ML model: NN
Proportion Train:Validation:Test = 63:17:20

WEAK

The model has a score of 5/10

- •• The test set shows an R^2 of 0.93
- - The test set has 22.2% of outliers
- - The test set uses 37:13 points:descriptors
- ••• The test set passes 3 VERIFY tests

Train : R^2 = 0.97, MAE = 0.056, RMSE = 0.11
Validation : R^2 = 0.99, MAE = 0.062, RMSE = 0.078
Test : R^2 = 0.93, MAE = 0.15, RMSE = 0.19

PFI (only important descriptors):

ML model: NN
Proportion Train:Validation:Test = 63:17:20

MODERATE

The model has a score of 8/10

- •• The test set shows an R^2 of 0.99
- •• The test set has 0.0% of outliers
- • The test set uses 37:6 points:descriptors
- ••• The test set passes 3 VERIFY tests

Train : R^2 = 0.96, MAE = 0.076, RMSE = 0.13
Validation : R^2 = 0.98, MAE = 0.087, RMSE = 0.11
Test : R^2 = 0.99, MAE = 0.064, RMSE = 0.081

Score thresholds

R^2	Outliers	Points:descriptors	VERIFY tests
•• R^2 > 0.85	•• < 7.5% of outliers	•• > 10:1 p:d ratio	Up to •••• (tests pass)
• 0.85 > R^2 > 0.70	• 7.5% < outliers < 15%	• 10:1 > p:d ratio > 3:1	- (all tests failed)
- R^2 < 0.70	- > 15% of outliers	- p:d ratio < 3:1	

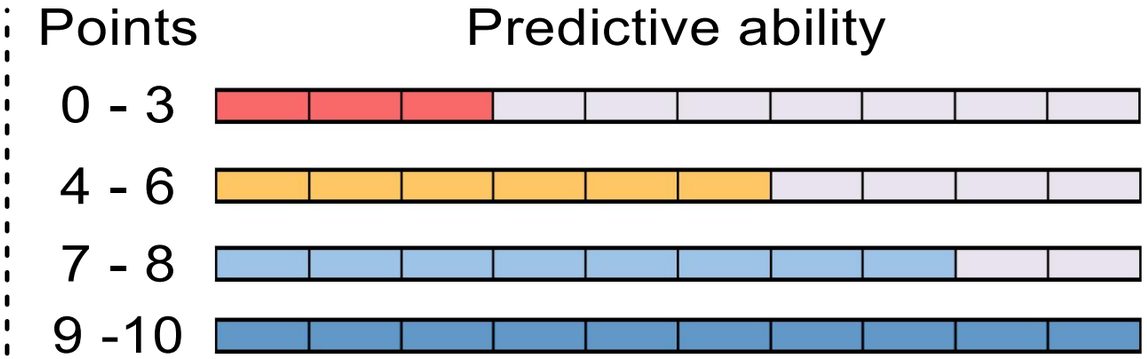
ROBERT v 1.0.3 — Page 1 of 7

ROBERT: automation of ML protocols

Score criteria (points)

Points	R^2	Outliers	Desc:pts
●●	> 0.85	< 7.5%	> 1:10
●	0.70 - 0.85	7.5 - 15%	1:3 - 1:10
–	< 0.70	> 15%	< 1:3

Verify tests (up to ●●●●)		
	● 5-fold CV	● y-shuffle
	● y-mean	● One-hot



No PFI (all descriptors):

WEAK

Your model has a score of **5/10**

●● Your model shows an R^2 of 0.93
- Your model has 22.2% of outliers
- Your model uses 37:13 points:descriptors
●●● Your model passes 3 VERIFY tests

PFI (only important descriptors):

MODERATE

Your model has a score of **8/10**

●● Your model shows an R^2 of 0.99
●● Your model has 0.0% of outliers
● Your model uses 37:6 points:descriptors
●●● Your model passes 3 VERIFY tests

ROBERT: automation of ML protocols

Some tips to improve the score

⚠ The model uses only 37 datapoints, adding meaningful datapoints might help to improve the model.

⚠ One of your models have more than 7.5% of outliers (5% is expected for a normal distribution with the t-value of 2 that ROBERT uses), using a more homogeneous distribution of results might help. For example, avoid using many points with similar y values and only a few points with distant y values.

⚠ Adding meaningful descriptors or replacing/deleting the least useful descriptors used might help. Feature importances are gathered in the SHAP and PFI sections of the /PREDICT/PREDICT_data.dat file.

How to predict new values with these models?

1. Create a CSV database with the new points, including the necessary descriptors.

2. Place the CSV file in the parent folder (i.e., where the module folders were created)

3. Run the PREDICT module as 'python -m robert --predict --csv_test FILENAME.csv'.

4. The predictions will be stored in the last column of two CSV files called MODEL_SIZE_test(_No)_PFI.csv, which are stored in the PREDICT folder.

No PFI (all descriptors):

WEAK

Your model has a score of **5/10**

●● Your model shows an R^2 of 0.93
- Your model has 22.2% of outliers
- Your model uses 37:13 points:descriptors
●●● Your model passes 3 VERIFY tests

PFI (only important descriptors):

MODERATE

Your model has a score of **8/10**

●● Your model shows an R^2 of 0.99
●● Your model has 0.0% of outliers
● Your model uses 37:6 points:descriptors
●●● Your model passes 3 VERIFY tests

Reproducibility and transparency

REPRODUCIBILITY

This section provides all the instructions to reproduce the results presented.

1. Download these files *(the authors should have uploaded the files as supporting information!)*:

- Report with results (ROBERT_report.pdf)
- CSV database (Robert_example.csv)
- External test set (Robert_example_test.csv)

2. Install the following Python modules:

- ROBERT: conda install -c conda-forge robert=1.0.3 (or pip install robert==1.0.3)
- scikit-learn-intelex: pip install scikit-learn-intelex==2023.2.1
- To generate the ROBERT_report.pdf summary, the following libraries might be necessary:

  WeasyPrint: pip install weasyprint==59.0

  GLib: conda install -c conda-forge glib

  Pango: conda install -c conda-forge pango

  GTK3: conda install -c conda-forge gtk3

3. Run ROBERT with this command line in the folder with the CSV databases (originally run in Python 3.10.12):

```
python -m robert --csv_test "Robert_example_test.csv" --csv_name "Robert_example.csv" --y "Target_values" --names "Name"
```

4. Provide number and model of processors used to achieve:

Total execution time: 101.98 seconds

TRANSPARENCY

This section contains important parameters used in scikit-learn models and ROBERT.

1. Parameters of the scikit-learn models (same keywords as used in scikit-learn):

No PFI (all descriptors):	PFI (only important descriptors):
sklearn model: MLPRegressor	sklearn model: MLPRegressor
random_state: 0	random_state: 0
batch_size: 8	batch_size: 8
hidden_layer_sizes: [16, 16]	hidden_layer_sizes: [16, 16]
learning_rate_init: 0.01	learning_rate_init: 0.01
max_iter: 50	max_iter: 50
validation_fraction: 0.3	validation_fraction: 0.3
alpha: 0.0001	alpha: 0.0001
shuffle: True	shuffle: True
tol: 0.0001	tol: 0.0001
early_stopping: False	early_stopping: False
beta_1: 0.9	beta_1: 0.9
beta_2: 0.999	beta_2: 0.999
epsilon: 1e-08	epsilon: 1e-08

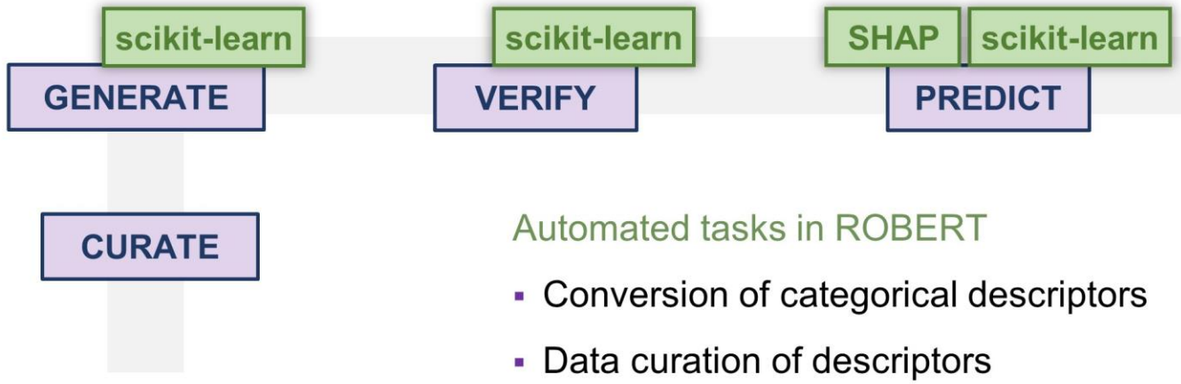
2. ROBERT options for data split (KN or RND), predict type (REG or CLAS) and hyperopt error (RMSE, etc.):

No PFI (all descriptors):	PFI (only important descriptors):
split: KN	split: KN
type: reg	type: reg
error_type: rmse	error_type: rmse

ROBERT: automation of ML protocols

Full workflow from csv

Only one command line required



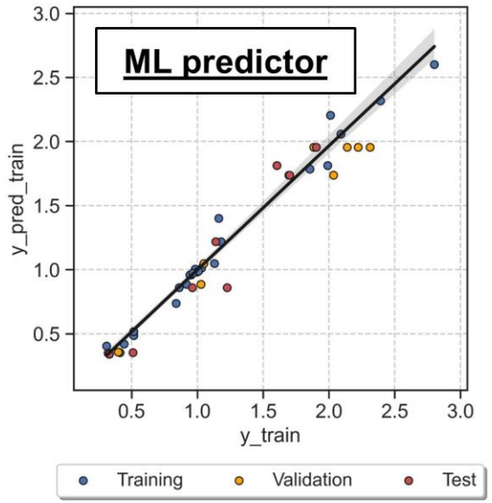
Input: CSV database

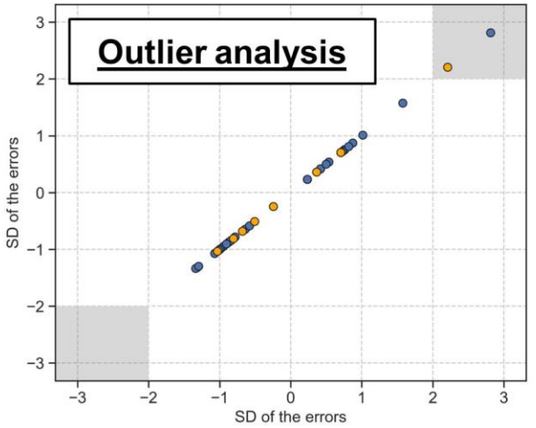
Name	y	x1	x2
Point_1	1.85	12	10.9
Point_2	2.03	11.7	10.7
Point_3	0.86	-23.05	12.1
Point_4	1.03	-16.24	12.1
Point_5	0.95	-31.94	11.9
Point_6	0.31	-68.04	13.1
Point_7	0.98	-34.71	10.8

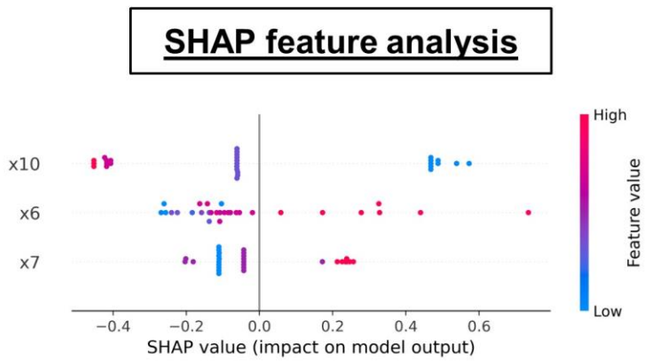
Automated tasks in ROBERT

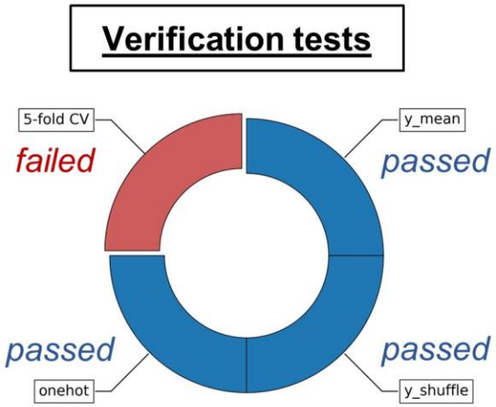
- Conversion of categorical descriptors
- Data curation of descriptors
- Screening of hyperoptimized ML models
- Screening of partition sizes
- New models with relevant features (PFI)
- Prediction of test set (if any) & SHAP analysis
- Analysis of outliers across different sets
- Verification tests to ensure predictive ability

Outputs:







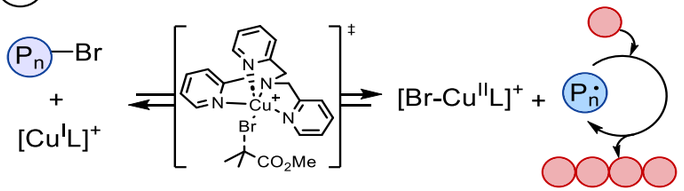


Only one command line: python -m robert --csv_name name.csv --y target_value

ROBERT: automation of ML protocols

ROBERT AUTOMATED ML PROTOCOLS

A Cu catalized polymerization (Liu, 2019)

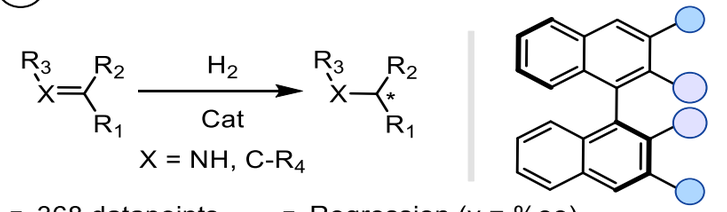


- 18 datapoints
- Regression (y = $\Delta G^{\ddagger}$)
- Training size: 50% (original), 70% (ROBERT)
- Number of descriptors: 3 (original), 1 (ROBERT)

B Ni photoredox catalysis (Doyle, 2021)

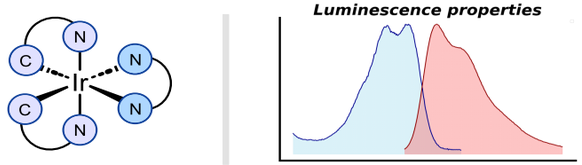
- 29 datapoints
- Regression (y = $\Delta\Delta G^{\ddagger}$)
- Training size: 75% (original), 60% (ROBERT)
- Number of descriptors: 3 (original), 3 (ROBERT)

C Asymmetric hydrogenation (Sunoj, 2020)



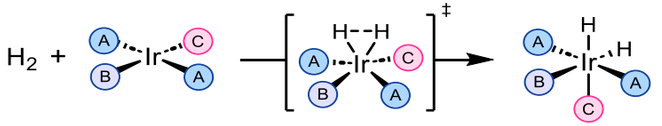
- 368 datapoints
- Regression (y = %ee)
- Training size: 80% (original), 70% (ROBERT)
- Number of descriptors: 101 (original), 2 (ROBERT)

D Ir photophysical properties (Kulik, 2023)



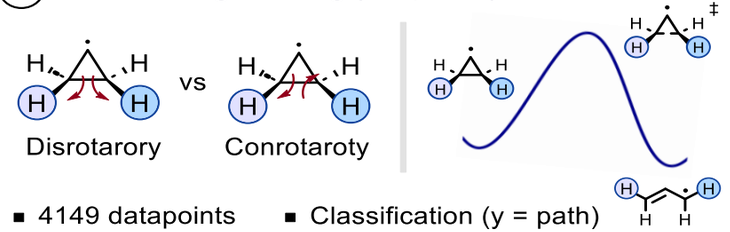
- 1173 datapoints
- Regression (y = spec. integ.)
- Training size: 70% (original), 76% (ROBERT)
- Number of descriptors: 12 (original), 11 (ROBERT)

E H_2 split (Aspuru-Guzik & Balcells, 2020)



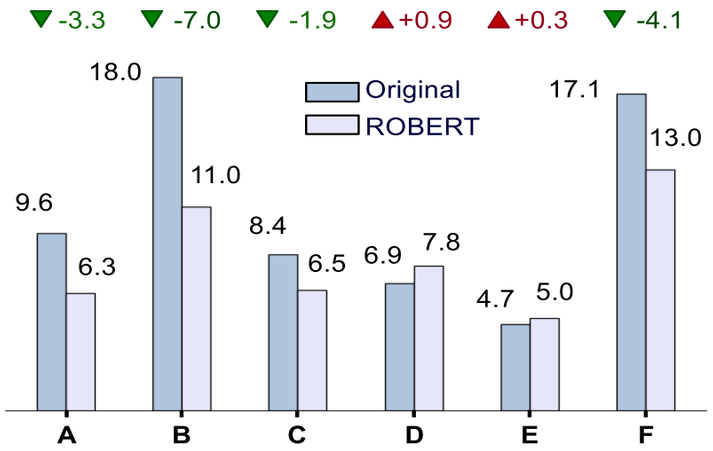
- 1947 datapoints
- Regression (y = $\Delta E^{\ddagger}$)
- Training size: 80% (original), 90% (ROBERT)
- Number of descriptors: 135 (original), 32 (ROBERT)

F Radical ring opening (Ess, 2021)



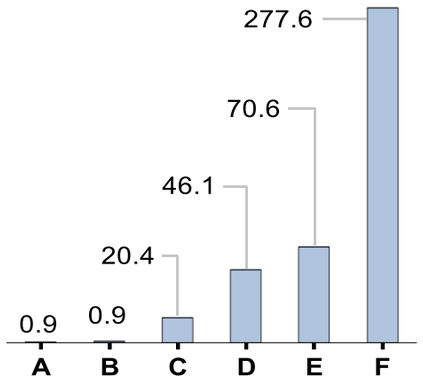
- 4149 datapoints
- Classification (y = path)
- Training size: 95% (original), 90% (ROBERT)
- Number of descriptors: 85 (original), 60 (ROBERT)

Scaled error (% total range)

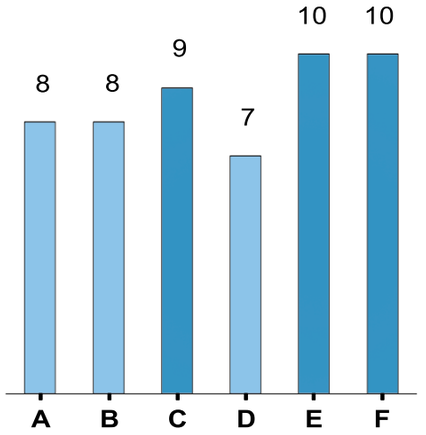


Execution time (minutes)

8 processors



ROBERT score



Score criteria (points)

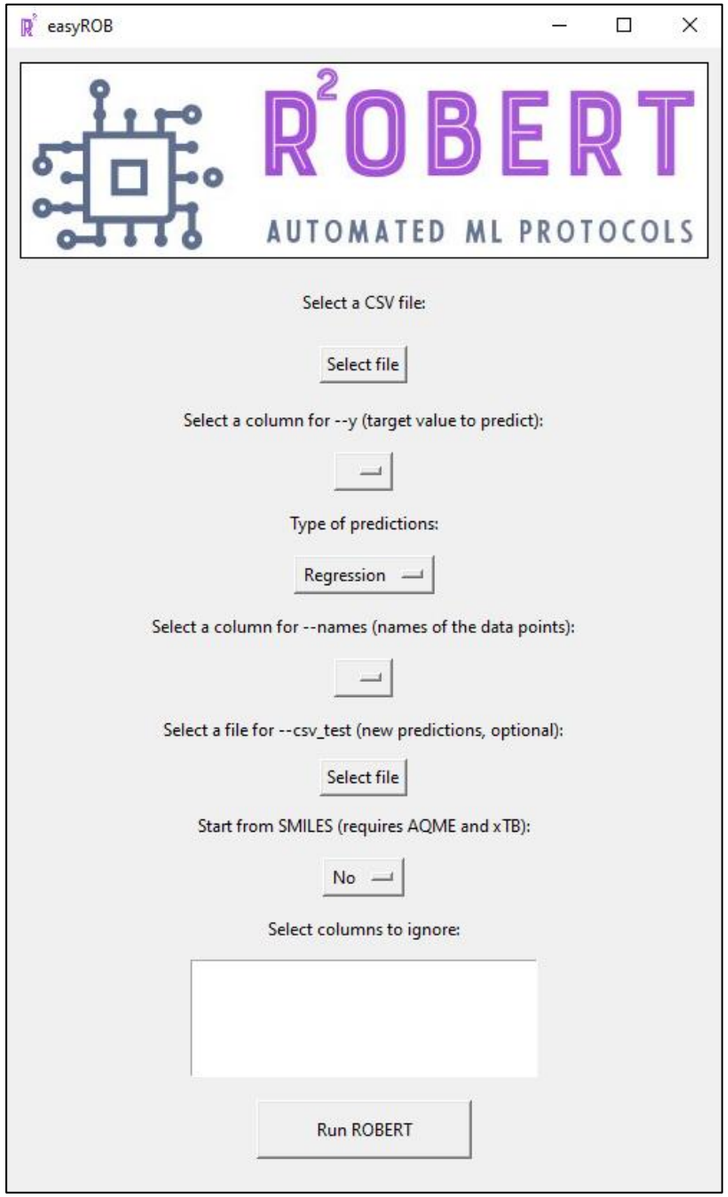
Points	R^2	Outliers	Desc:pts
●●	> 0.85	< 7.5%	< 1:3
●	0.70 - 0.85	7.5 - 15%	1:3 - 1:10
–	< 0.70	> 15%	> 1:10

Verify tests (up to ●●●●)		
● 5-fold CV	● y-shuffle	
● y-mean	● One-hot	

Points	Predictive ability
0 - 3	
4 - 6	
7 - 8	
9 -10	

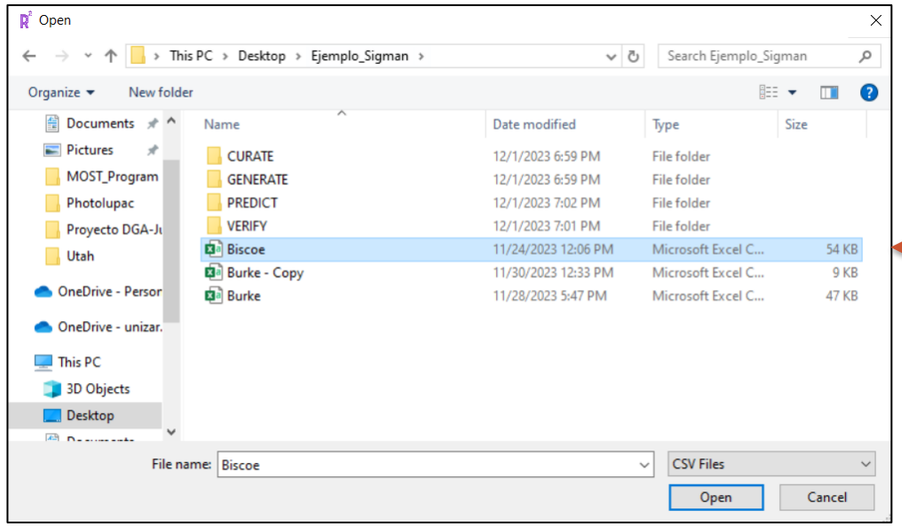
ROBERT: automation of ML protocols

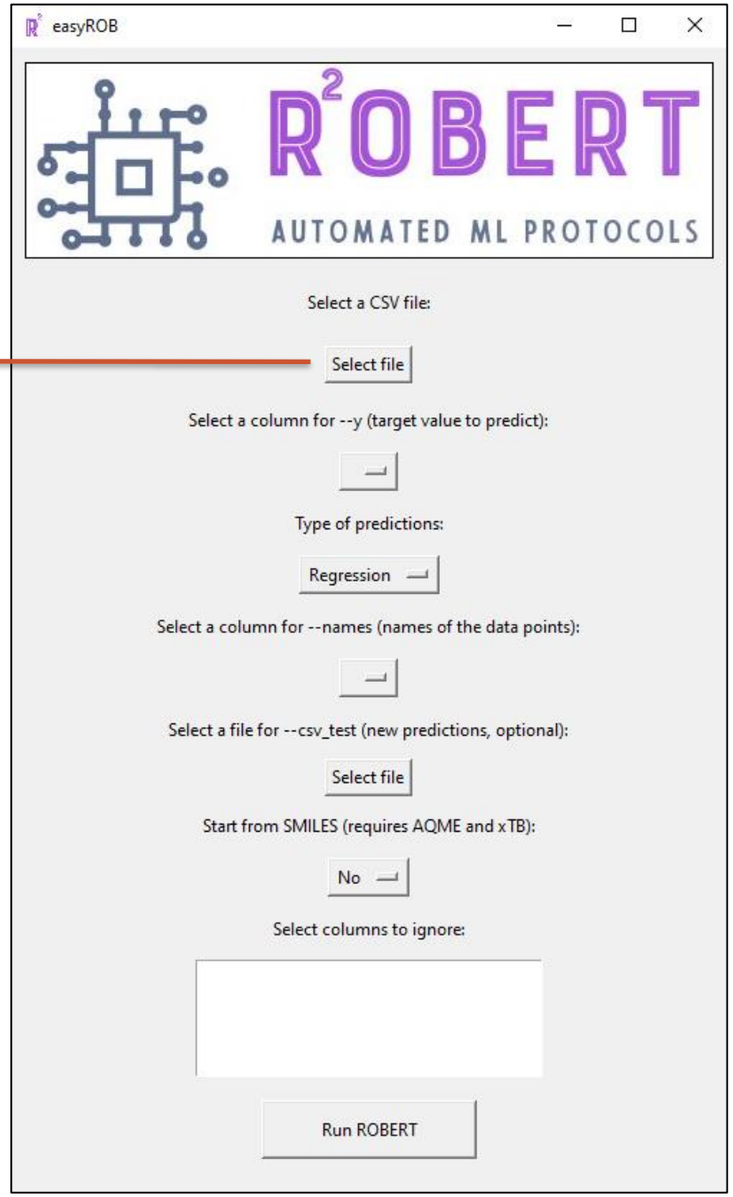
Graphical User Interface: easyROB



ROBERT: automation of ML protocols

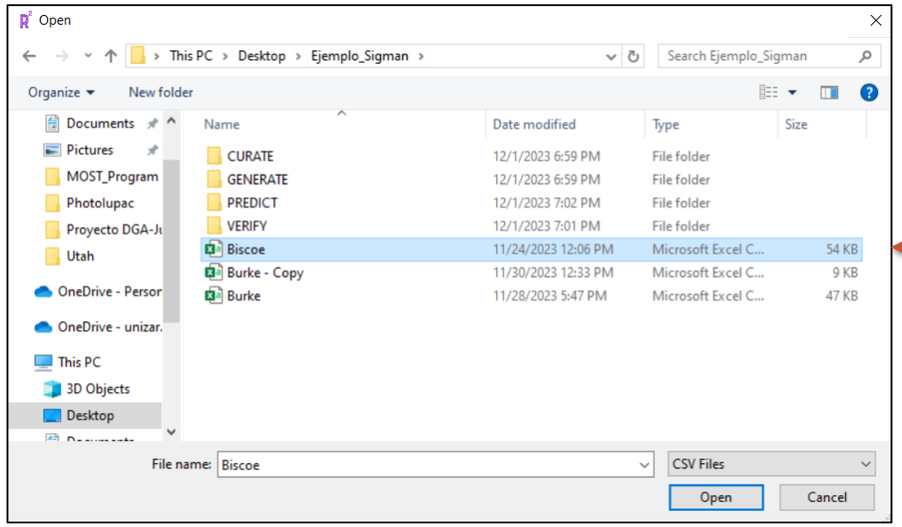
Graphical user interface: easyROB

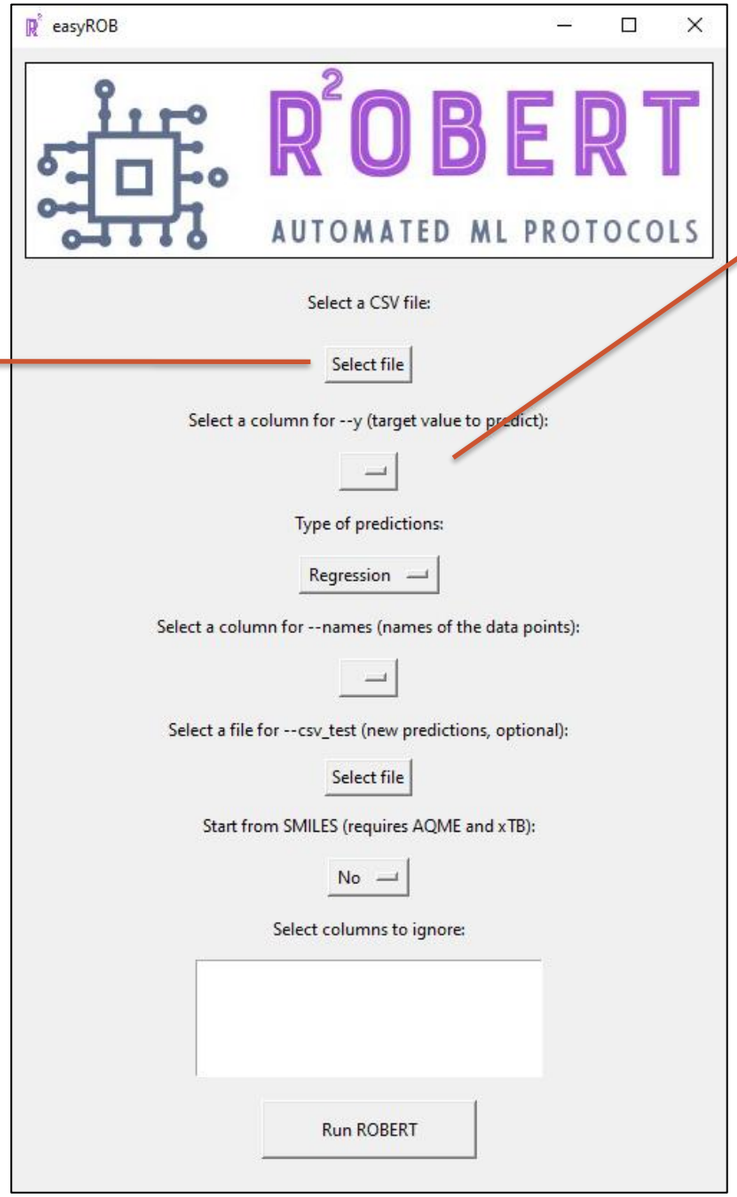


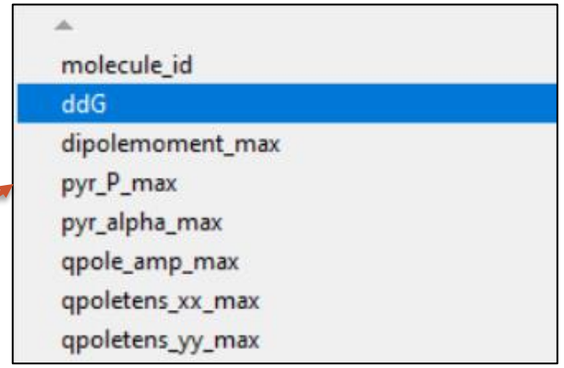


ROBERT: automation of ML protocols

Graphical user interface: easyROB

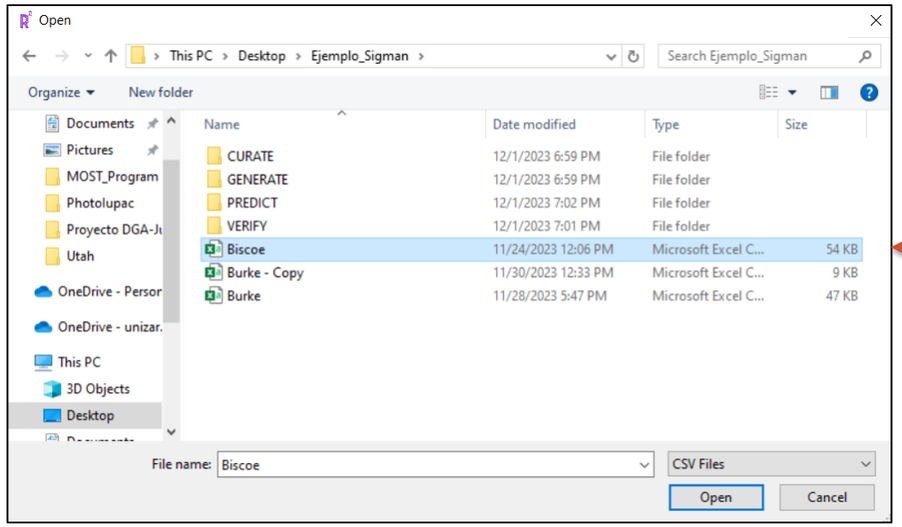


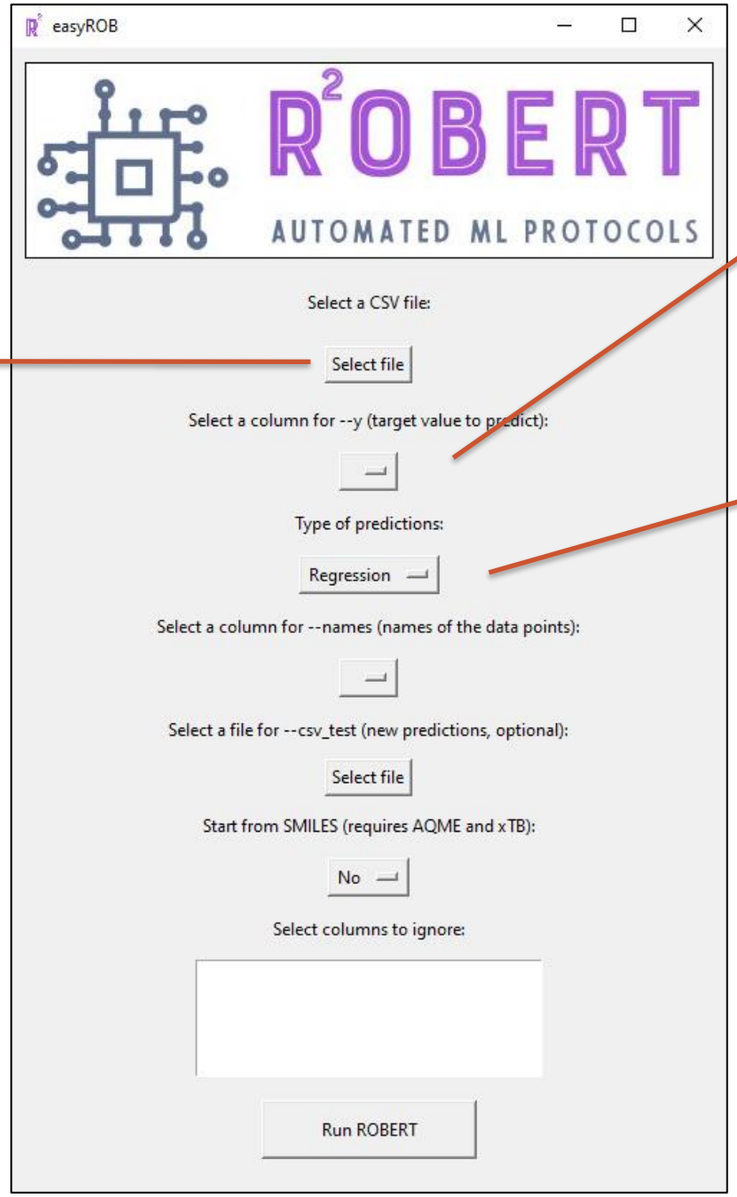


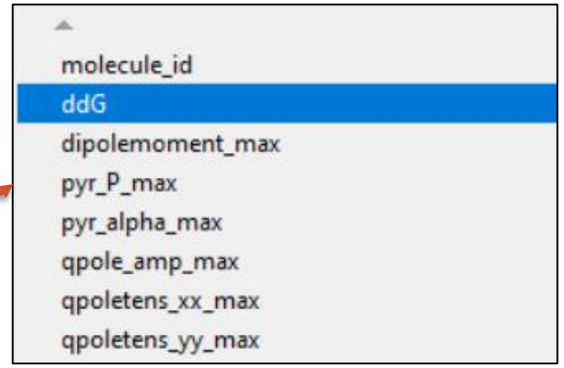


ROBERT: automation of ML protocols

Graphical user interface: easyROB

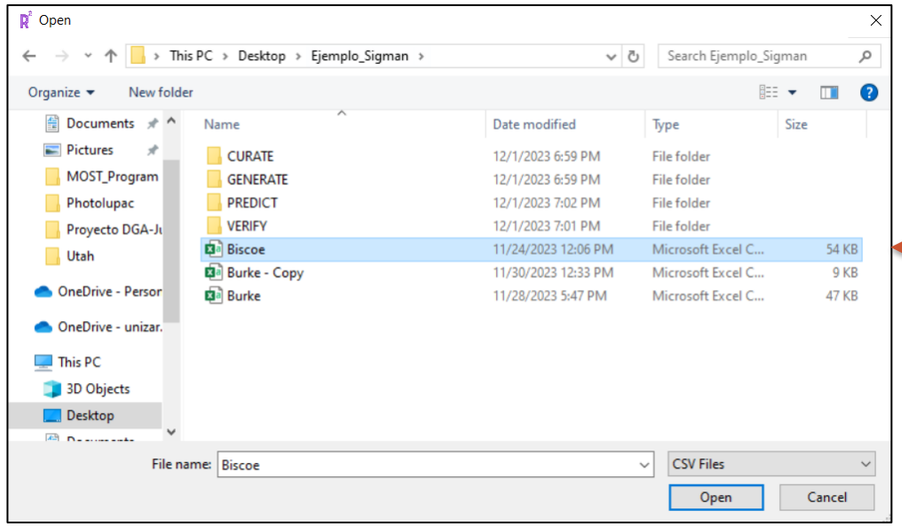


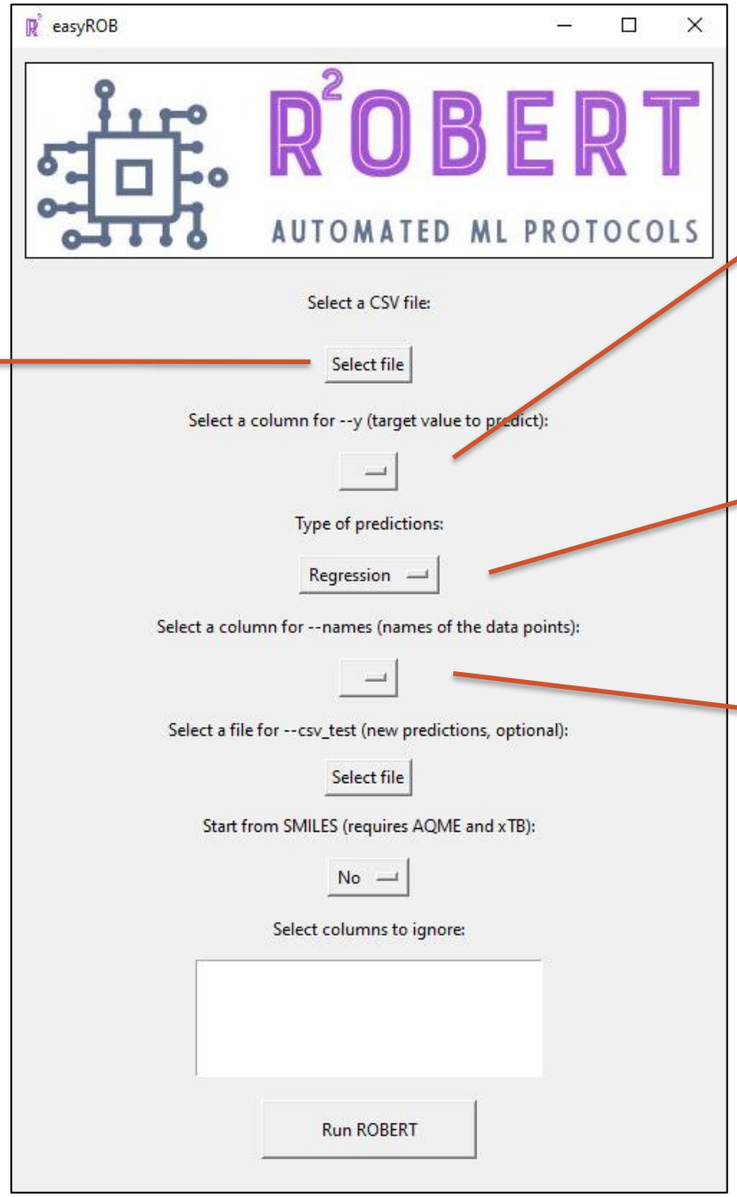


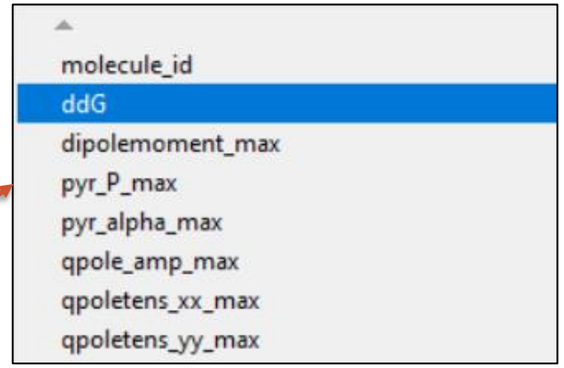


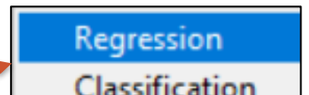
ROBERT: automation of ML protocols

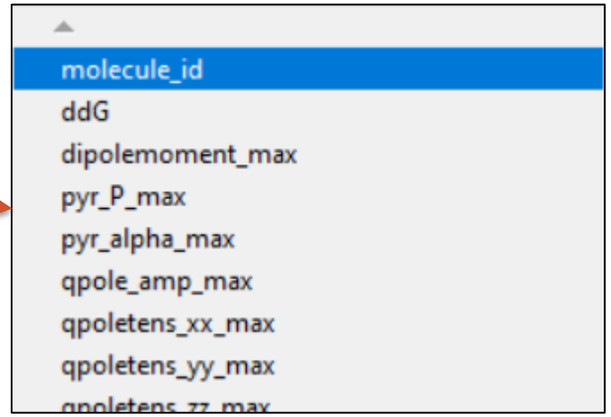
Graphical user interface: easyROB





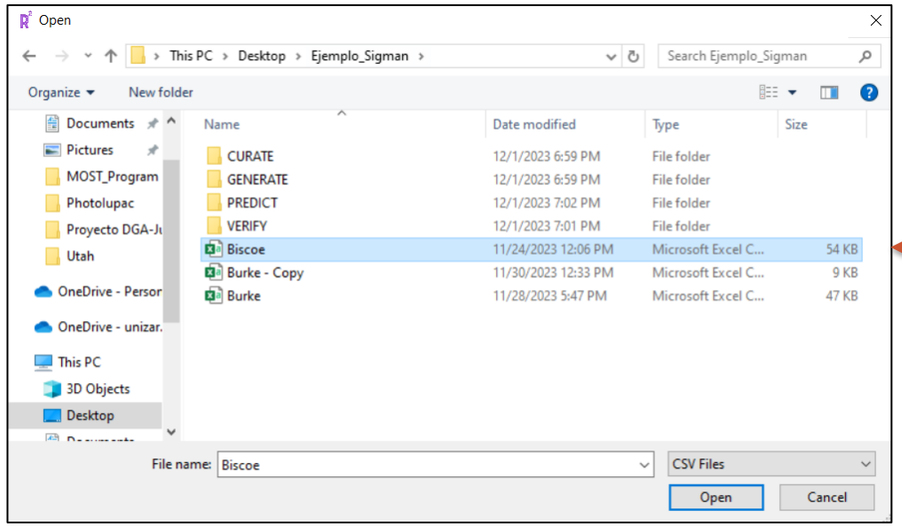


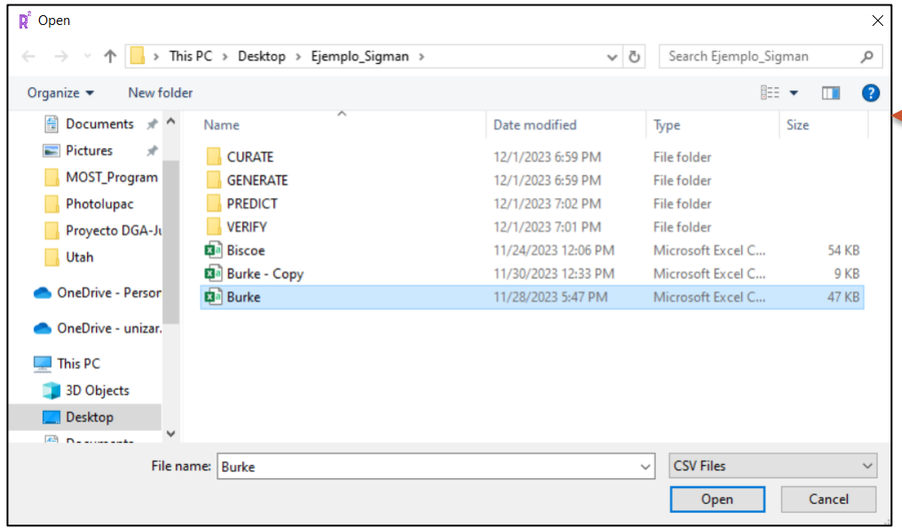


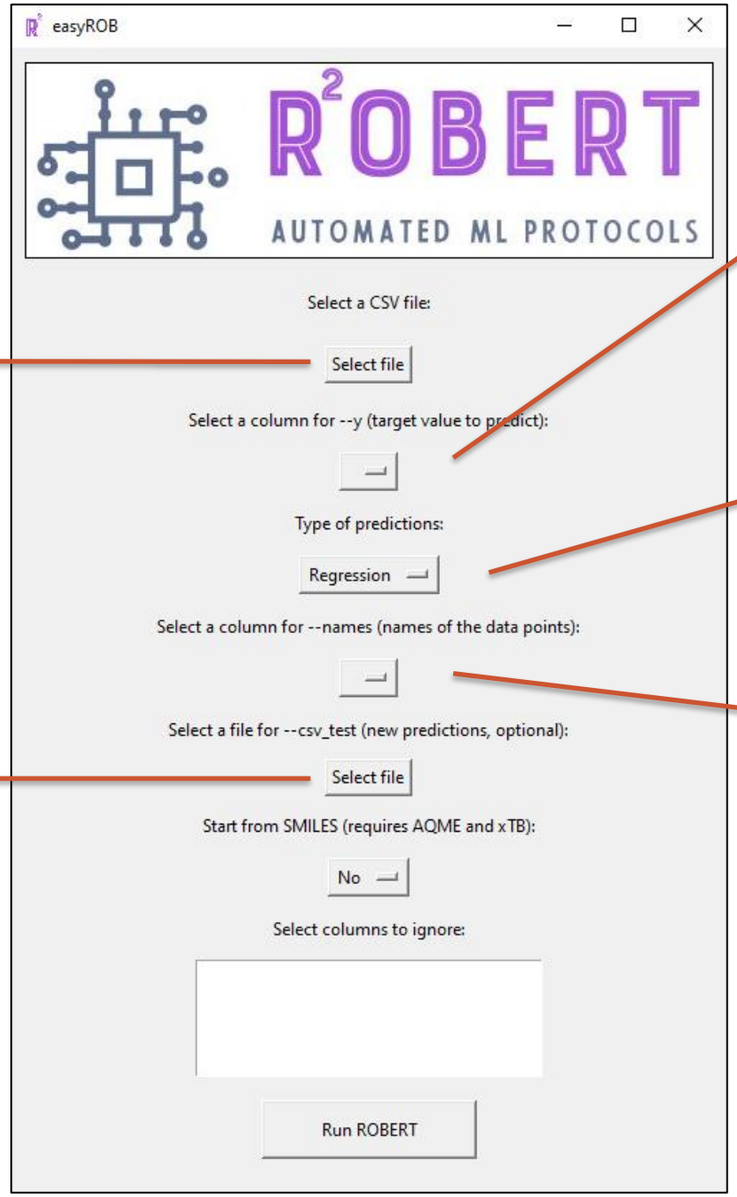


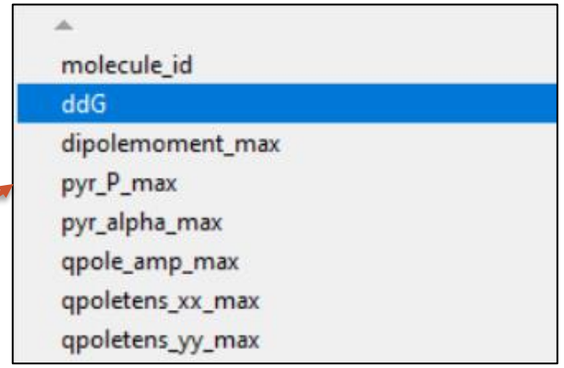
ROBERT: automation of ML protocols

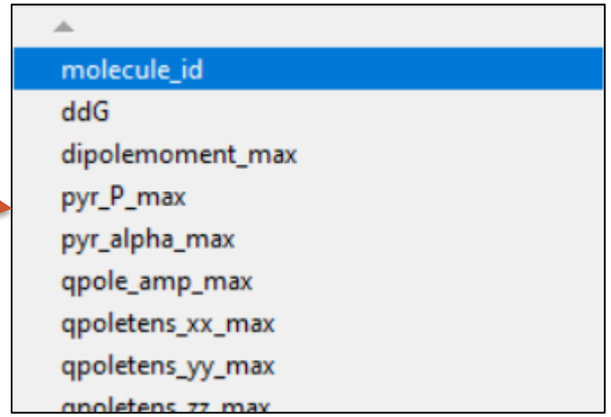
Graphical user interface: easyROB





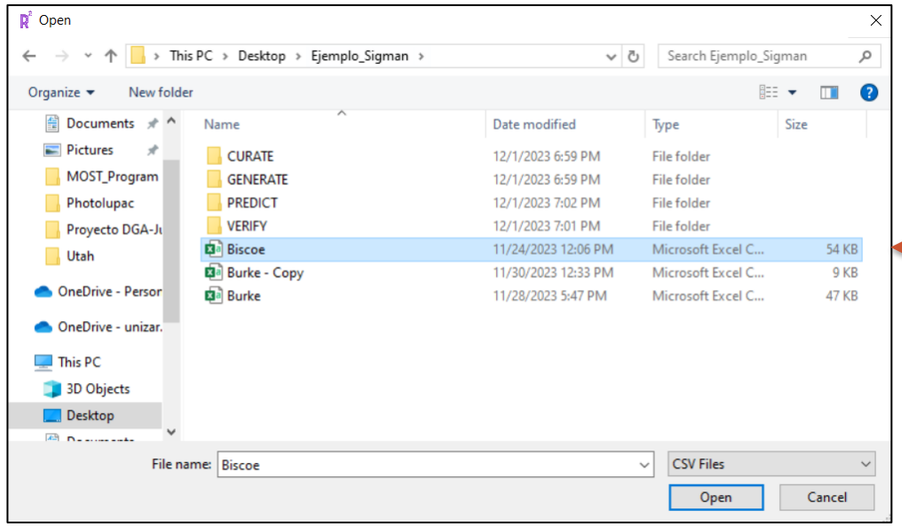


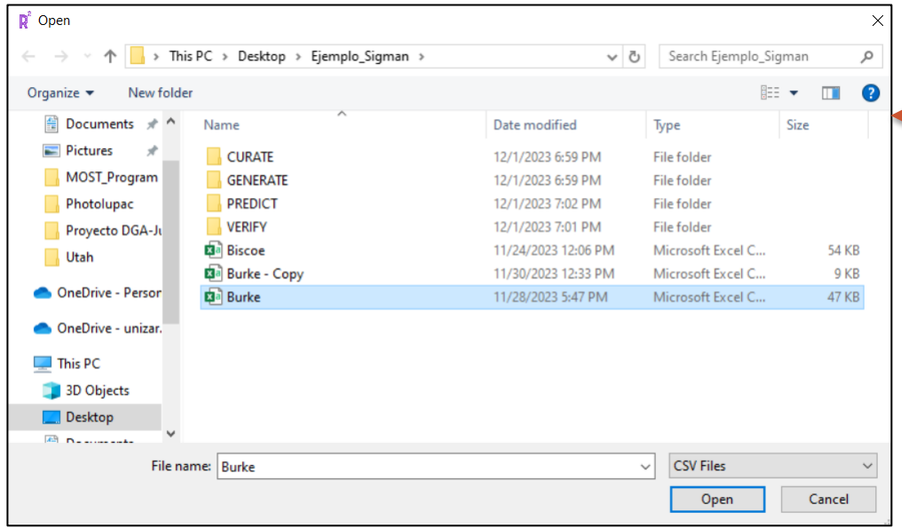


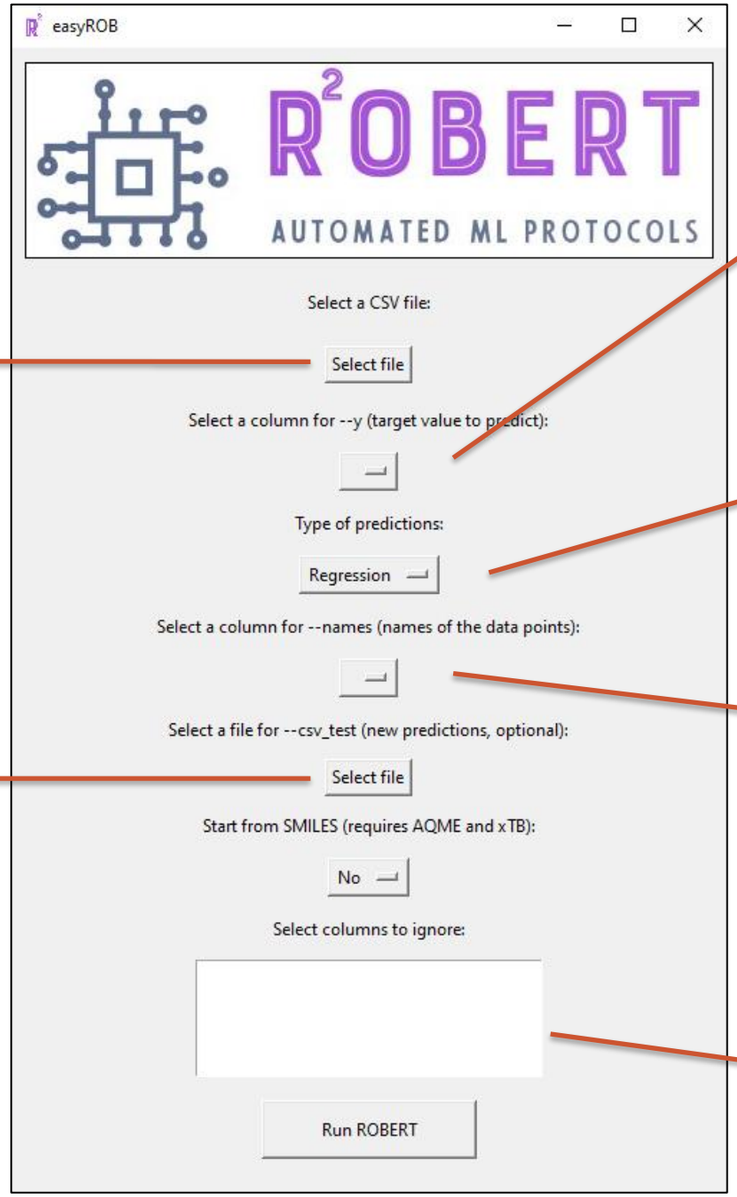


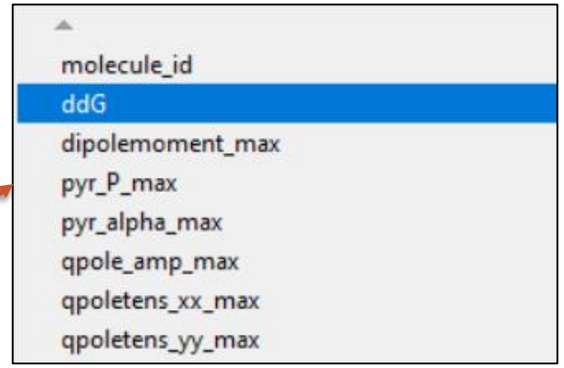
ROBERT: automation of ML protocols

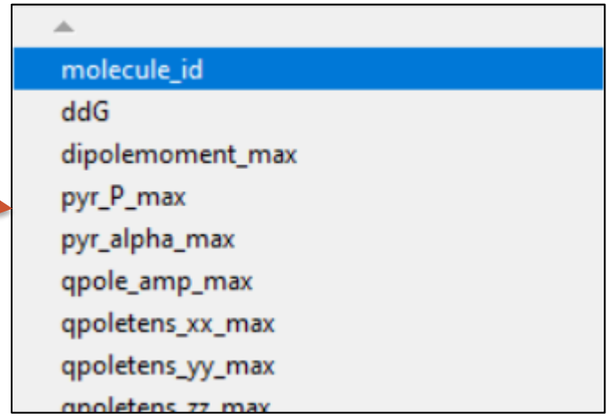
Graphical user interface: easyROB

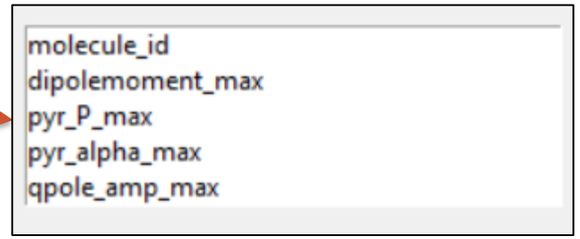












AQME+ROBERT

Automated generation of ML predictors

+

R²OBERT
AUTOMATED ML PROTOCOLS

AQME+ROBERT

Automated generation of ML predictors

+

R²OBERT
AUTOMATED ML PROTOCOLS

Only one command line: python -m robert --csv_name name.csv --y target_value --aqme

AQME+ROBERT

Automated generation of ML predictors

+

R²ROBERT
AUTOMATED ML PROTOCOLS

Initial AQME workflow

Input: CSV with SMILES

CSV database

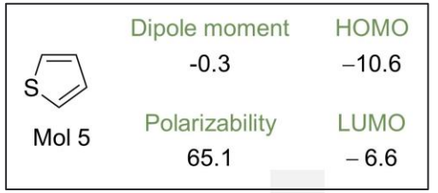
SMILES	code_name	solub.
c1ccsc1	mol_5	-1.33
CCCC=C	mol_13	-2.68
CC(C)Cl	mol_16	-1.41
ClC(=C)Cl	mol_34	-1.64

RDKit CSEARCH → xTB RDKit QDESCP

- 200+ RDKit molecular descriptors
- 12 xTB molecular descriptors
- 16 xTB atomic descriptors *(if any)*
- DBSTEP's Buried volume *(if any)*

Automated tasks in AQME

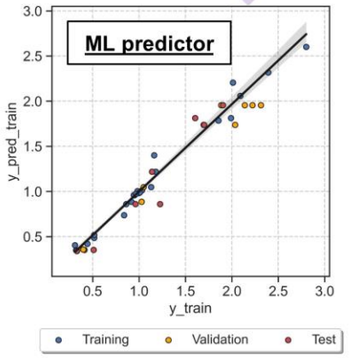
- Conformational search with RDKit
- Molecular featurization using xTB & RDKit
- Boltzmann averaging of descriptors
- Creation of a CSV database for ROBERT

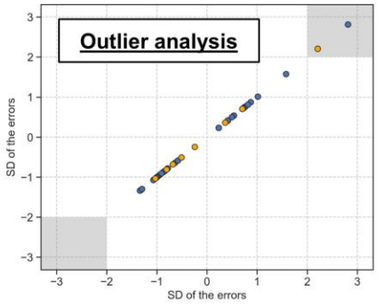


CSV

One command line

Outputs:



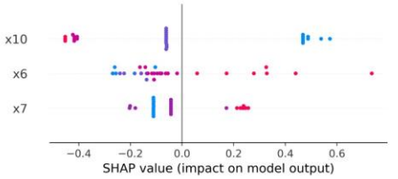


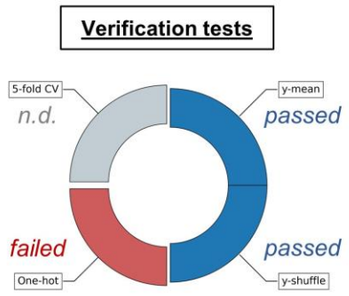
Coupled ROBERT workflow

CURATE → scikit-learn GENERATE → scikit-learn VERIFY → SHAP scikit-learn PREDICT

Automated tasks in ROBERT

- Data curation of RDKit/xTB descriptors
- Screening of hyperoptimized ML models
- Screening of partition sizes
- New models with relevant features (PFI)
- Prediction of test set (if any) & SHAP analysis
- Analysis of outliers across different sets
- Verification tests to ensure predictive ability





Only one command line: python -m robert --csv_name name.csv --y target_value --aqme

AQME+ROBERT

Automated generation of ML predictors

ESOL: Estimating Aqueous Solubility Directly from Molecular Structure

John S. Delaney

View Author Information

Cite this: *J. Chem. Inf. Comput. Sci.* 2004, 44, 3, 1000−1005

Publication Date: March 13, 2004

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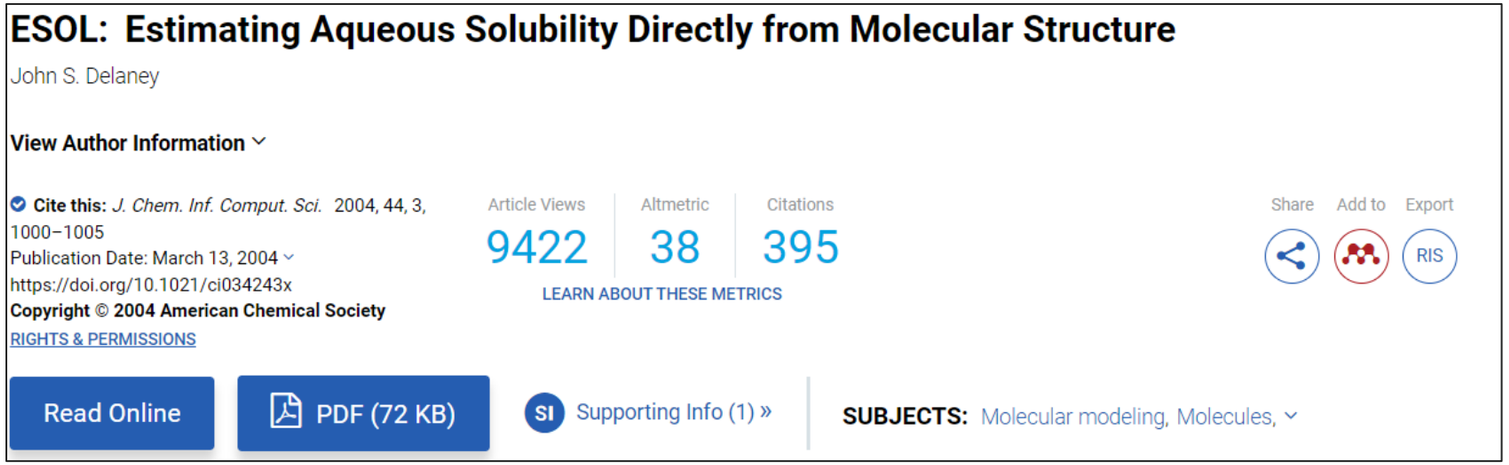
SUBJECTS: Molecular modeling, Molecules,

AQME+ROBERT

Automated generation of ML predictors

1 command line



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SUBJECTS: Molecular modeling, Molecules,

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1 command line

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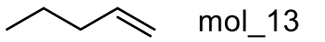
A Estimating aqueous solubility

Input: CSV with SMILES

ESOL database

SMILES	code_name	solub.
c1ccsc1	mol_5	-1.33
CCCC=C	mol_13	-2.68
CC(C)Cl	mol_16	-1.41
ClC(=C)Cl	mol_34	-1.64

AQME

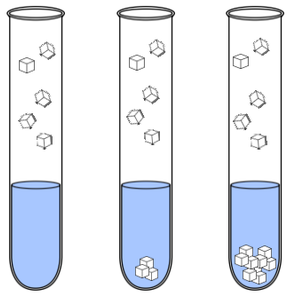


Conformer sampling

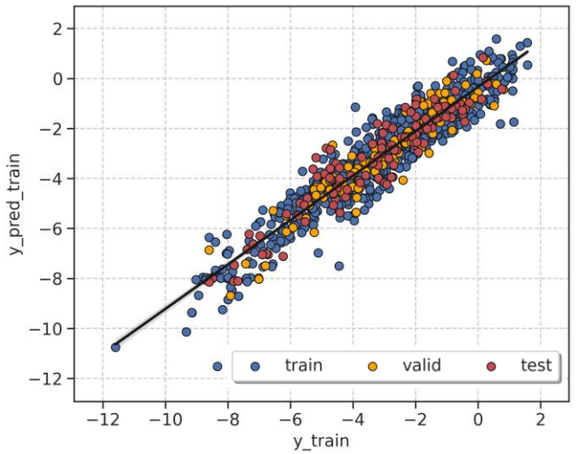
Mol. featurization

200+ RDKit, xTB and DBSTEP descriptors

ROBERT



Solubility prediction



ROBERT SCORE

ML model: MVL
Proportion Train:Validation:Test = 81:9:10

STRONG

The model has a score of 10/10

- The test set shows an R^2 of 0.89
- The valid. set has 4.9% of outliers
- Using 1012:47 points(train+valid.):descriptors
- The valid. set passes 4 VERIFY tests

Only one command line: python -m robert --csv_name solubility.csv --y solubility --aqme --qdescp_keywords "--qdescp_solvent h2o"

AQME+ROBERT

Automated generation of ML predictors

1 command line

ESOL: Estimating Aqueous Solubility Directly from Molecular Structure

John S. Delaney

View Author Information

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Publication Date: March 13, 2004
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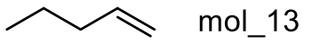

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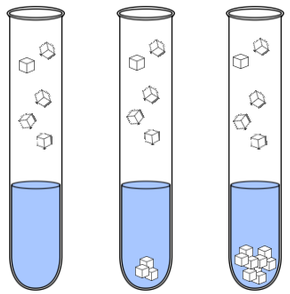

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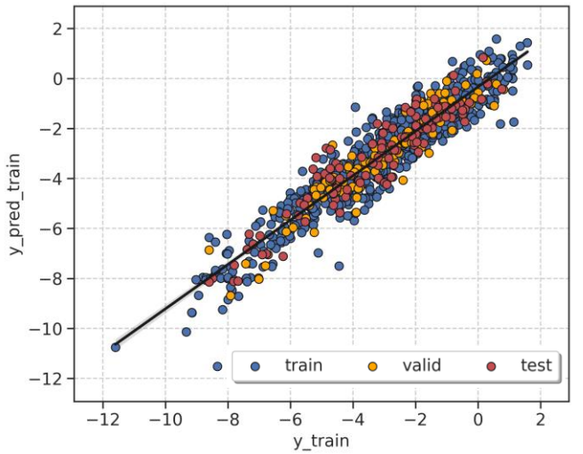

ROBERT SCORE

ML model: MVL
Proportion Train:Validation:Test = 81:9:10

STRONG

Train : R^2 = 0.89, MAE = 0.54, RMSE = 0.7
Validation : R^2 = 0.89, MAE = 0.53, RMSE = 0.68
Test : R^2 = 0.89, MAE = 0.59, RMSE = 0.74

Only one command line: python -m robert --csv_name solubility.csv --y solubility --aqme --qdescp_keywords "--qdescp_solvent h2o"

AQME+ROBERT

Automatic generation of predictors

Input: CSV with SMILES

SMILES	code_name	$\Delta E^{\ddagger}$
[Ir]([P+](CC)...	ir_tbp_1_dft-pet3...	8.9
[Ir]([P+](C)...	ir_tbp_1_dft-pme3...	6.5
[Ir]([As+](C)...	ir_tbp_1_dft-asme3...	17.9
[Ir]([n+]1ccn...	ir_tbp_1_dft-pyz...	22

Machine learning dihydrogen activation in the chemical space surrounding Vaska's complex†‡

Check for updates

Pascal Friederich, [abc] Gabriel dos Passos Gomes, [ac] Riccardo De Bin, [d] Alán Aspuru-Guzik *[acef] and David Balcells *[g]

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1 command line

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1 command line

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B **Application to catalysis: Estimating activation energies**

Input: CSV with SMILES

Vaska's complex database

SMILES	code_name	ΔE‡
[Ir]([P+](CC)...	ir_tbp_1_dft-pet3...	8.9
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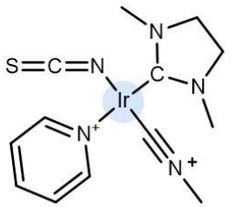
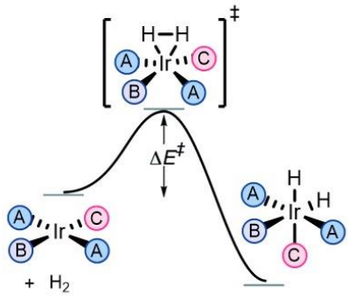
[Ir]([n+]1ccn...	ir_tbp_1_dft-pyz...	22

Step 1: AQME

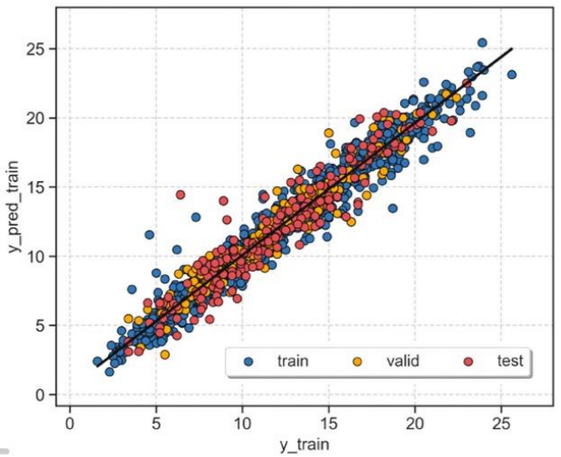


200+ electronic & steric atomic/molecular descps. (RDKit, xTB & DBSTEP)

Step 2: ROBERT



$\Delta E^{\ddagger}$ prediction



ROBERT SCORE

ML model: NN

Proportion Train:Validation:Test = 81:9:10

STRONG

The model has a score of 9/10

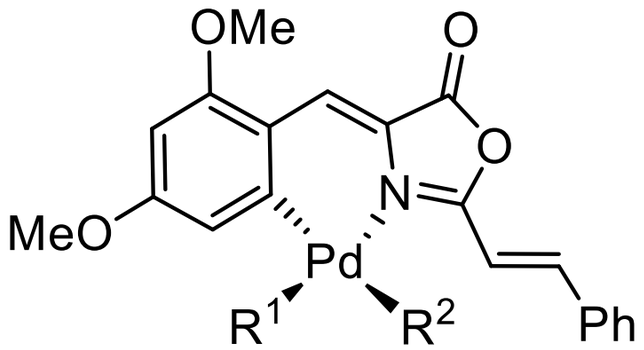
- ●● The test set shows an R^2 of 0.89
- ● The valid. set has 10.5% of outliers
- ●● Using 1711:21 points(train+valid.):descriptors
- ●●●● The valid. set passes 4 VERIFY tests

Only one command line: python -m robert --csv_name vaskas.csv --y barrier --aqme --qdescp_keywords "--qdescp_atoms [Ir]"

AQME+ROBERT

Real example of our lab

- Discovery of new Pd-oxazolone luminiscent compounds



1a: R^1 = Pyr, R^2 = TFA (18% QY)
1b: R^1 = Pyr, R^2 = Cl (12%)
1c: R^1 = Pyr, R^2 = Pyr (28%)
1d: R^1 = NHC, R^2 = TFA (15%)
1e: 8-Aminoquinoline (12%)

Eur. J. Org. Chem., **2018**, 6158-6166.

Molecules **2021**, *26*, 1238.

Org. Biomol. Chem., **2021**,19, 2773-2783

Inorg. Chem. **2023**, 62, 9792–9806.

From all the compounds reported across four articles, only five examples with QY > 10%!

AQME+ROBERT

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We could go to the lab and try new possible combinations

Experim.

AQME+ROBERT

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AQME+ROBERT

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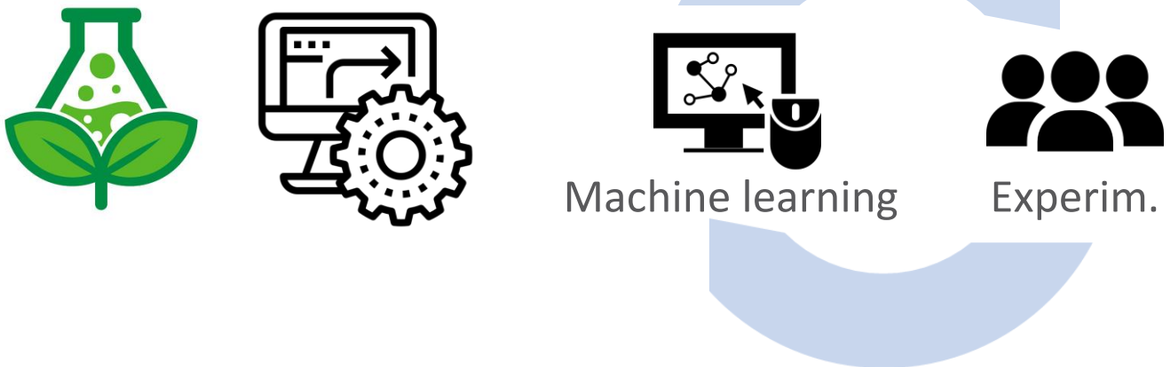

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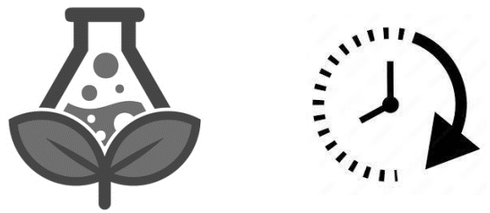
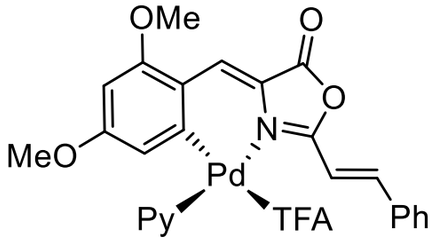
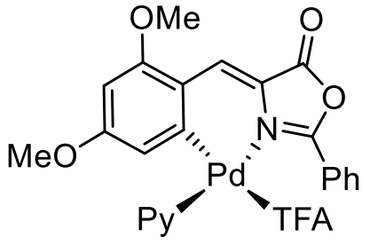


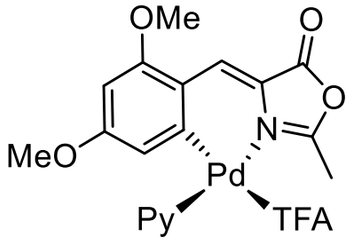
AQME+ROBERT

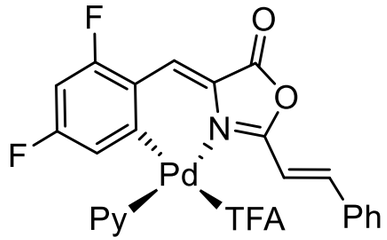
Real example of our lab

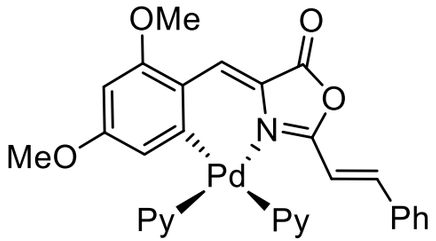
1. Draw in ChemDraw the 23 compounds that already exist

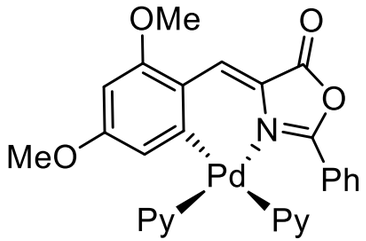


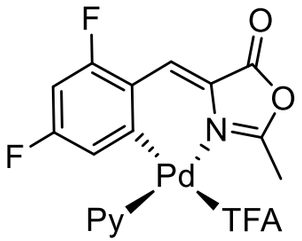


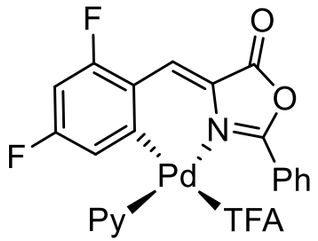












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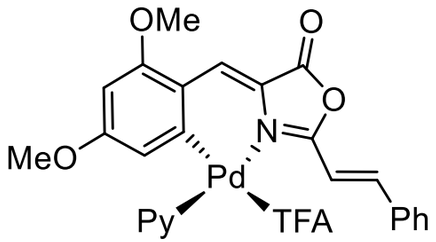

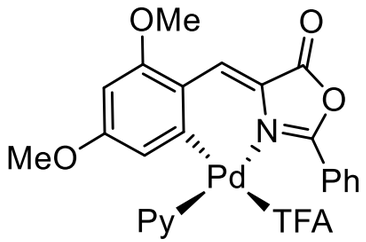

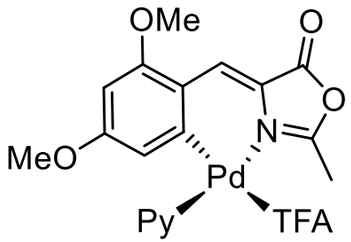

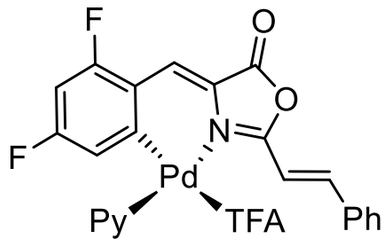

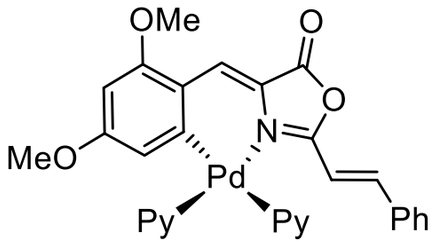

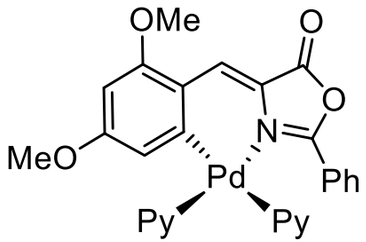

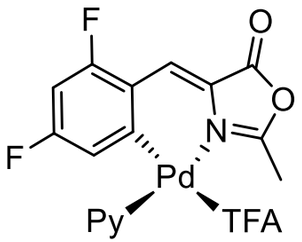

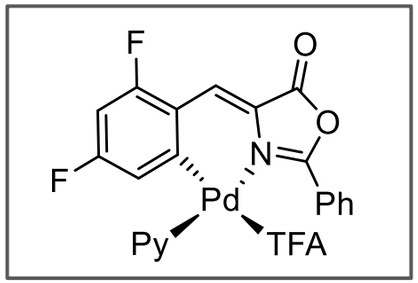

ccc(F)cc(F)C=C...

2. Convert the structures to SMILES strings (Ctrl + Alt + C)

Real example of our lab

3. Create the Excel database with names, SMILES and QY

code_name	SMILES	QY(%)
complex_1	O=C1OC=N/C1=C\C2...	2
complex_2	[Pd]C1=CC(OC)=CC(OC)...	5
complex_3	FC1=C2C([Pd][N]C=C2)...	12
...		

AQME+ROBERT

Real example of our lab

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...		

4. Run ROBERT

```
> python -m robert --y QY(%) --names code_name --aqme --csv Pd.csv
```

AQME+ROBERT

Real example of our lab

Aprox. 30-45 min

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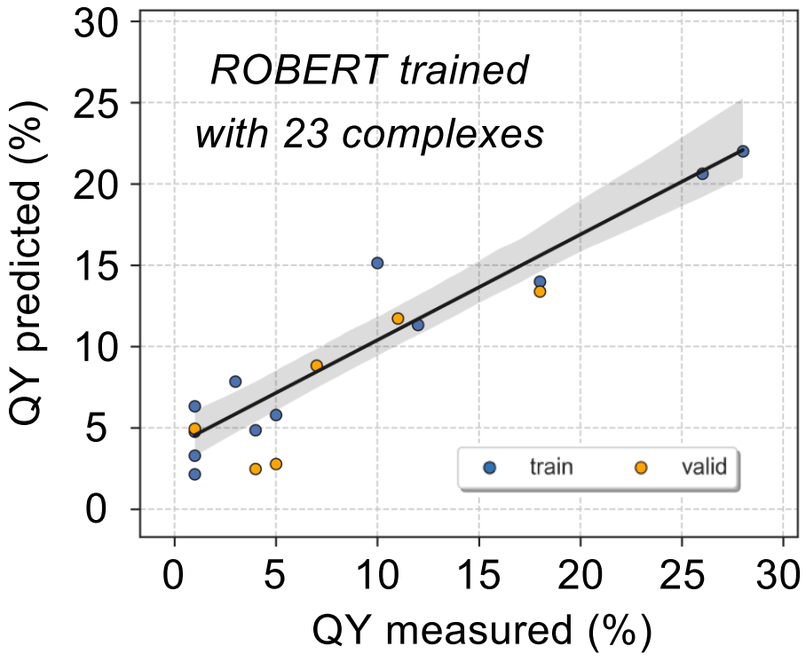


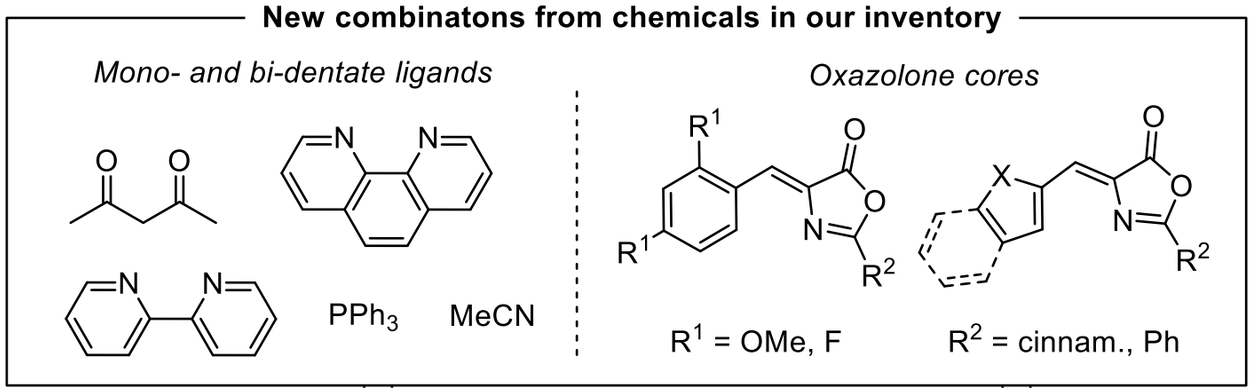
4. Run ROBERT

```
> python -m robert --y QY(%) --names code_name --aqme --csv Pd.csv
```

AQME+ROBERT

Real example of our lab

- ROBERT for predicting new candidates

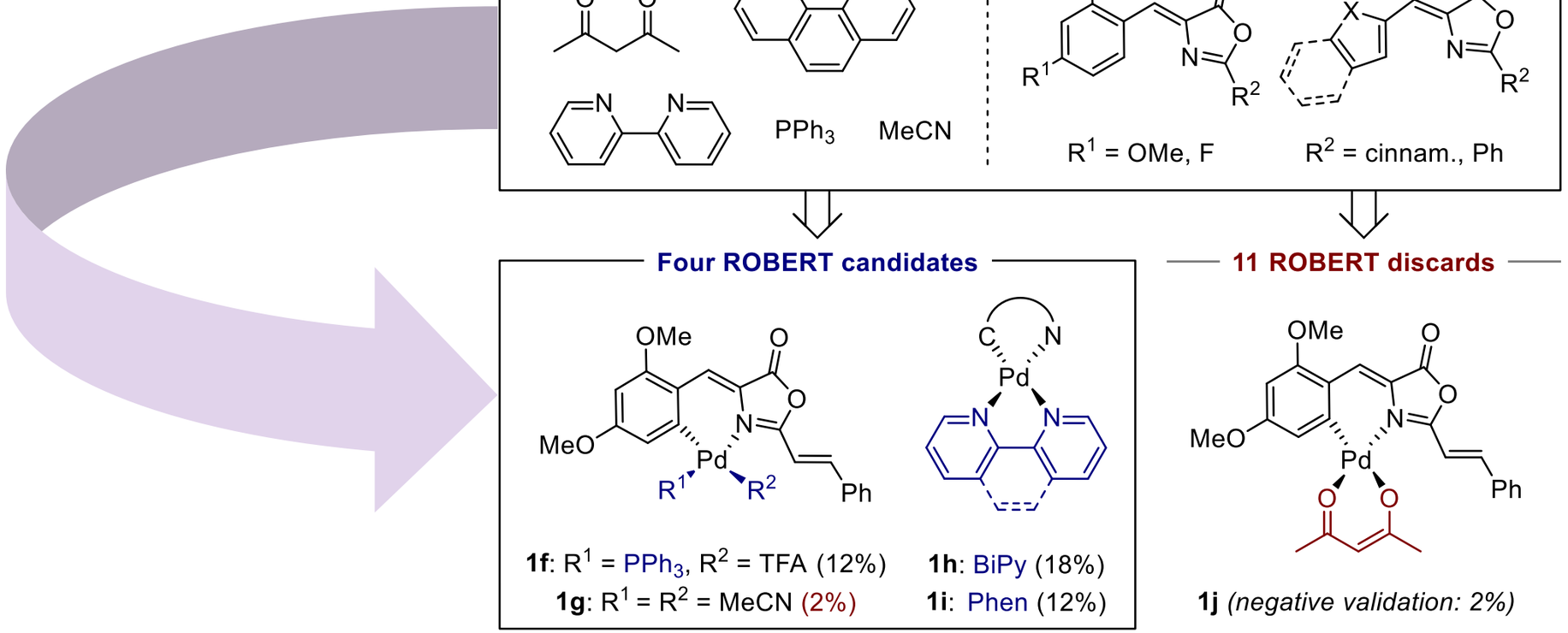


AQME+ROBERT

Real example of our lab

- ROBERT for predicting new candidates

Machine learning



AQME+ROBERT

Real example of our lab

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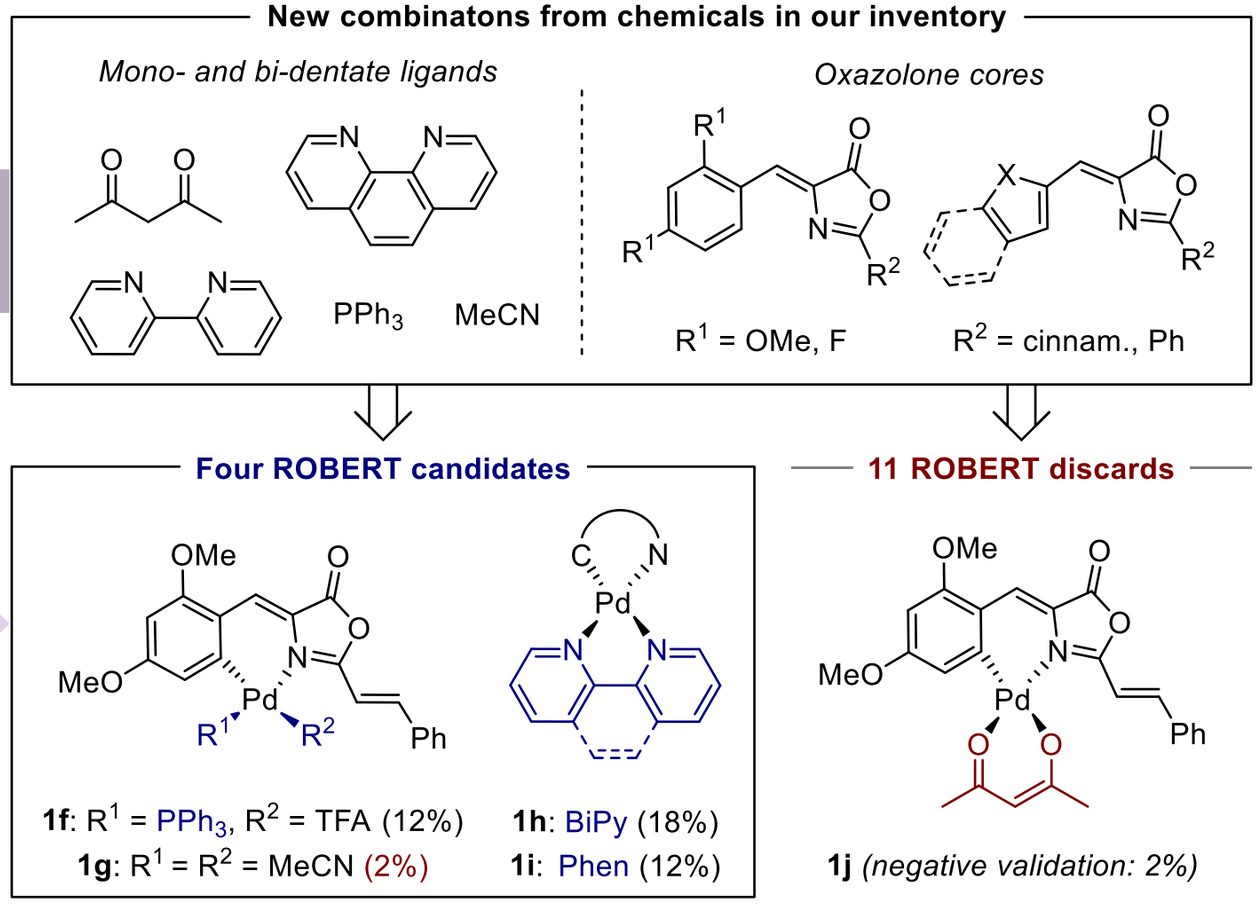
Machine learning



- Lab-tested: 80% Accuracy

ML to predict chemical outcomes

David Dalmau Ginesta

29/05/2025

IQCC