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IBM

Centre for Research Training

Science Foundation Ireland sfi For what's next

UCD DUBLIN University College Dublin University for All

How to generalize machine learning models to both canonical and non-canonical peptides

Speaker: **Raúl Fernández-Díaz (PhD Candidate UCD – IBM Research)**

UCD: R. Cossio-Pérez, C. Agoni, D.C. Shields

IBM Research: T.L. Hoang, V. Lopez

Novo Nordisk: R. Ochoa

Part 0 - Introduction

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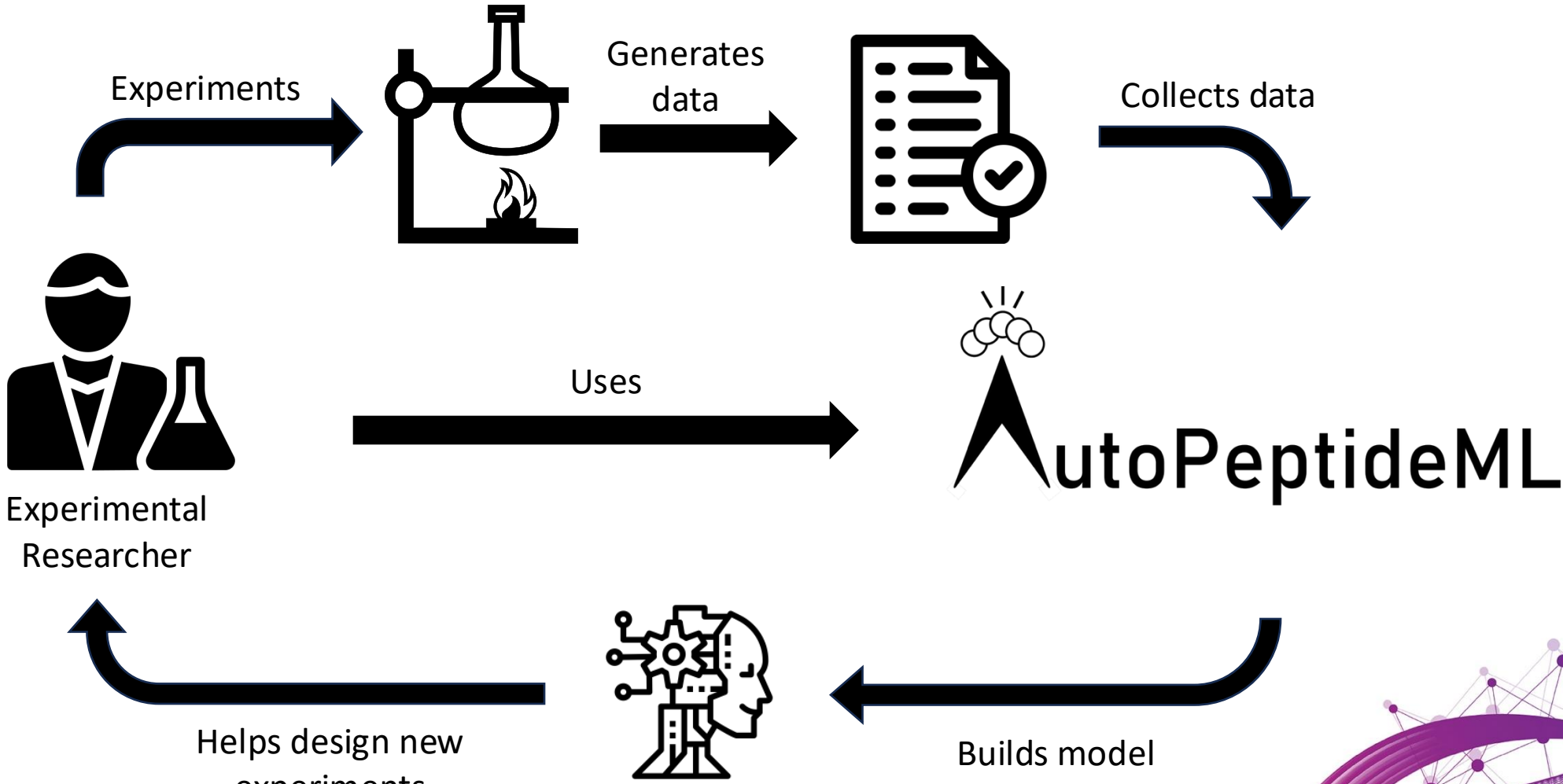
Main objective



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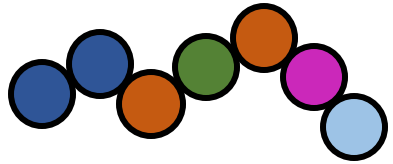
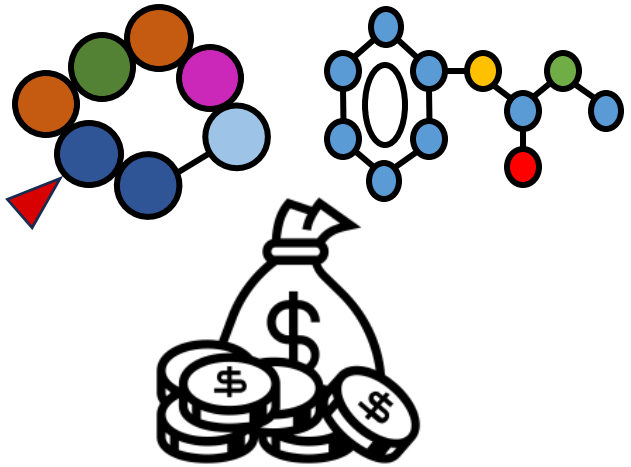
A tale of two peptides

Natural (or canonical) peptides
(cheap)



Synthetic peptides (or non-canonical) and peptidomimetics
(expensive but better drugs)



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Can we leverage data on cheaper experiments to prioritise more expensive experiments?

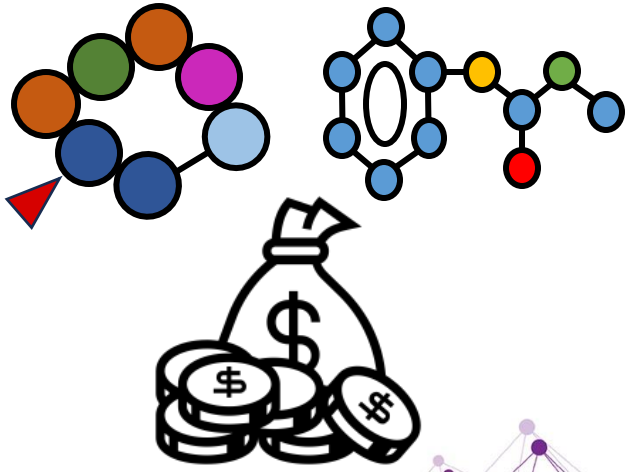
Natural peptides
(cheap)

Train

AutoPeptideML

Predict

Synthetic peptides and peptidomimetics
(expensive but better drugs)



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Objectives

1. How to automatically build peptide property prediction models (and evaluate them)
2. How to extrapolate from standard to modified peptides or peptidomimetics

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Part 1 – Automating ML for natural peptides

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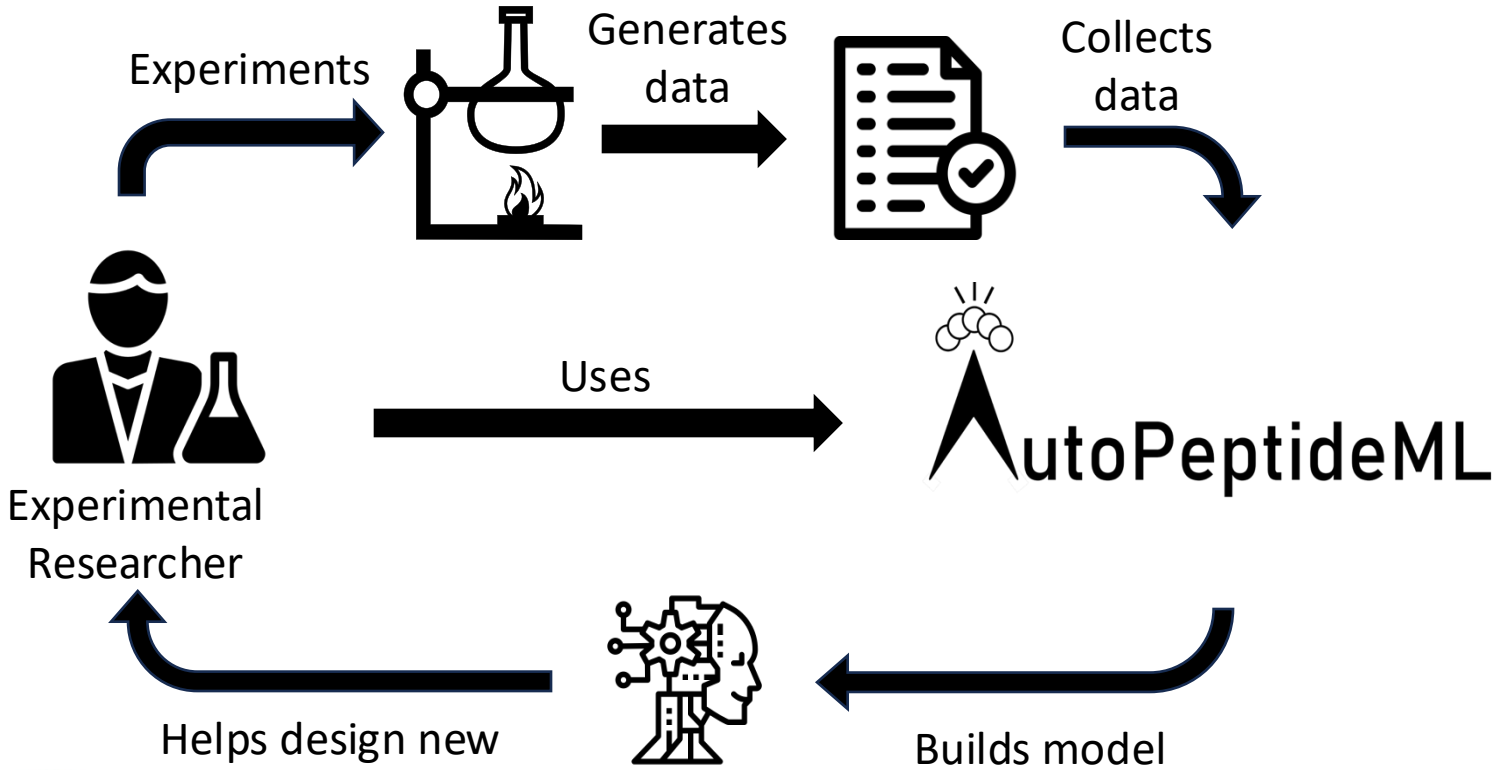
Objectives

AutoPeptideML

R. Fernández-Díaz et al., AutoPeptideML: a study on how to build more trustworthy peptide bioactivity predictors, *Bioinformatics*, Volume 40, Issue 9, September 2024, btae555



Design Requirements

1. Easy to use
2. Competitive performance
3. Reliable evaluation so that experimental scientist can trust the models

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Automating ML for natural peptides

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Collected **18** datasets used for building different peptide bioactivity predictors

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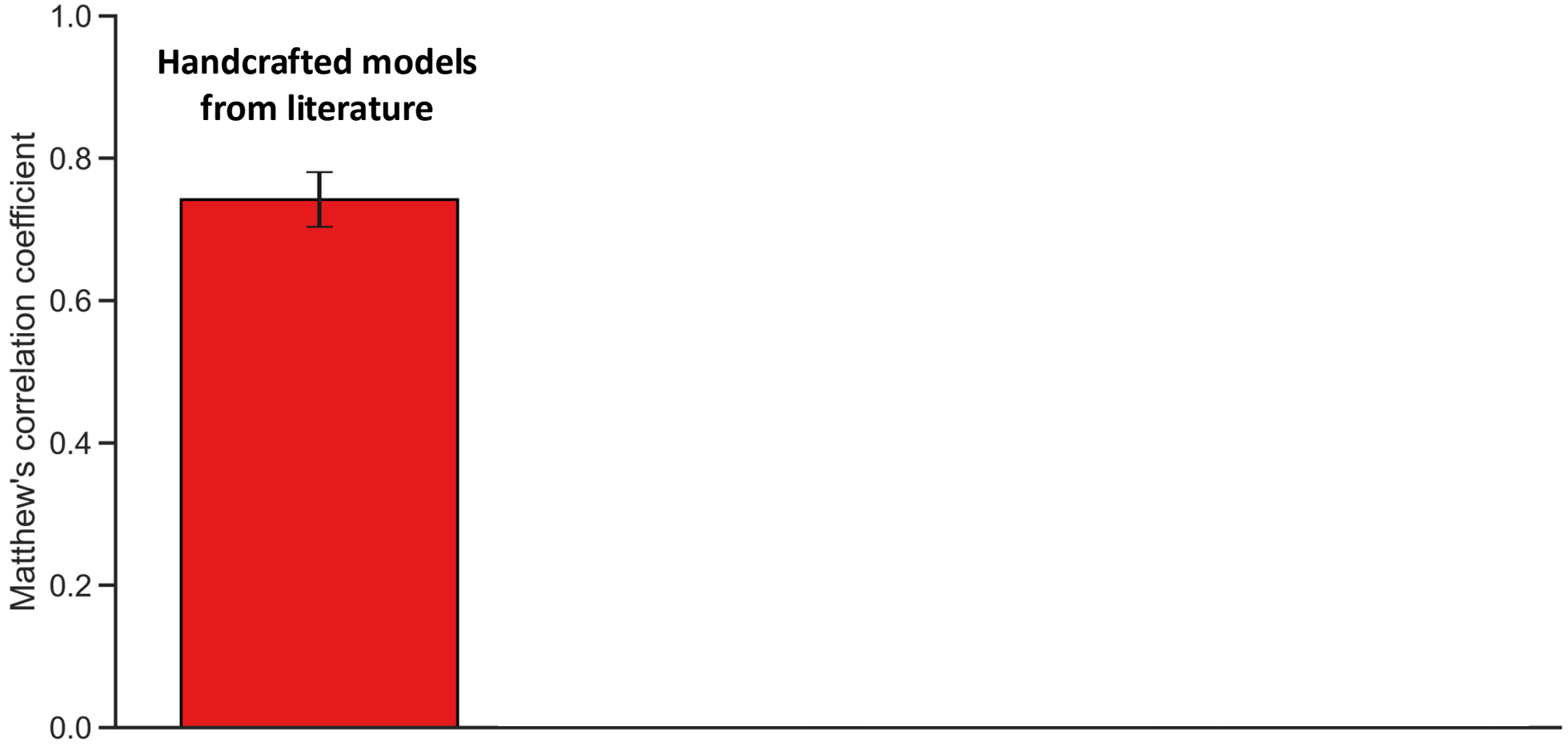

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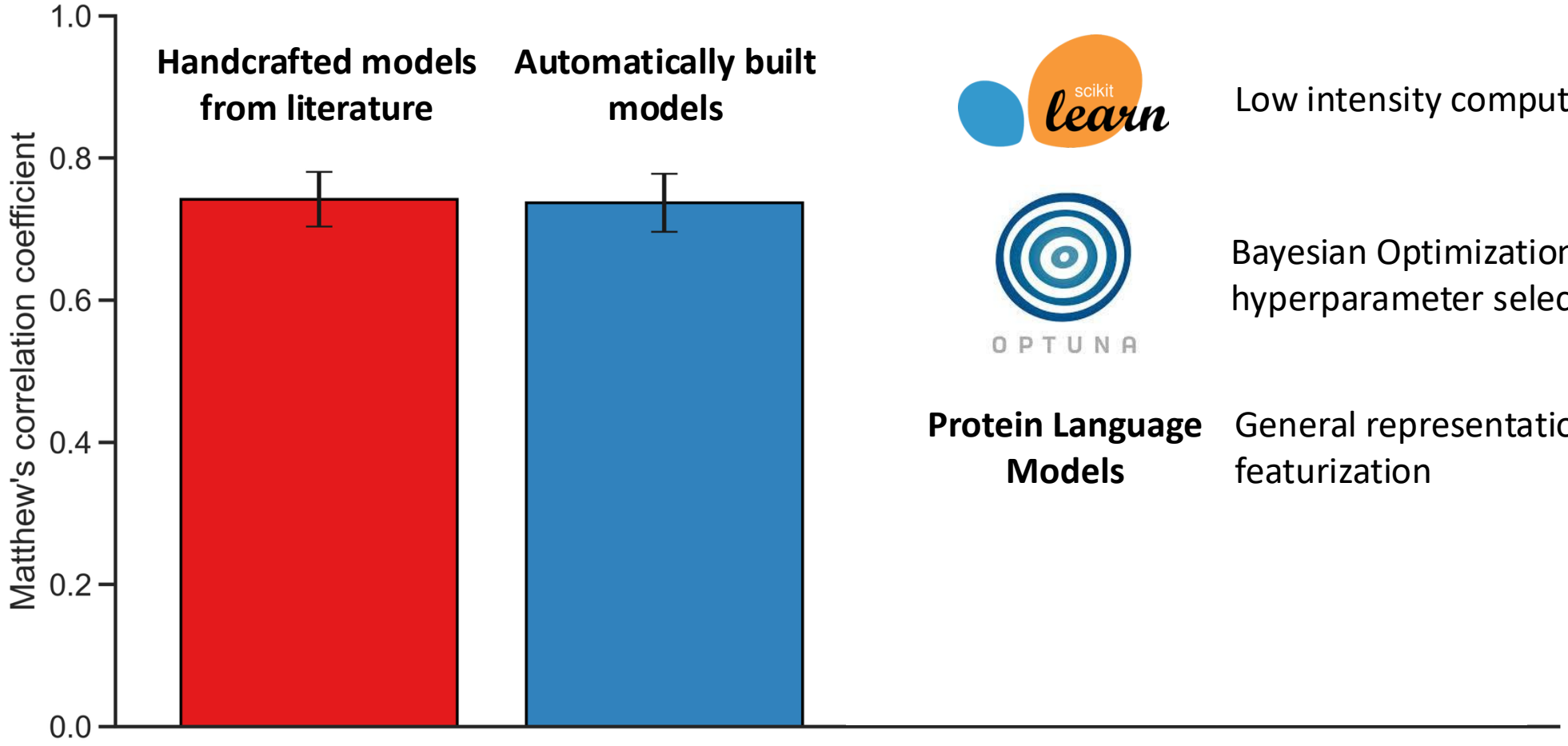

scikit learn — Low intensity computing

OPTUNA — Bayesian Optimization for hyperparameter selection

Protein Language Models — General representation/ featurization

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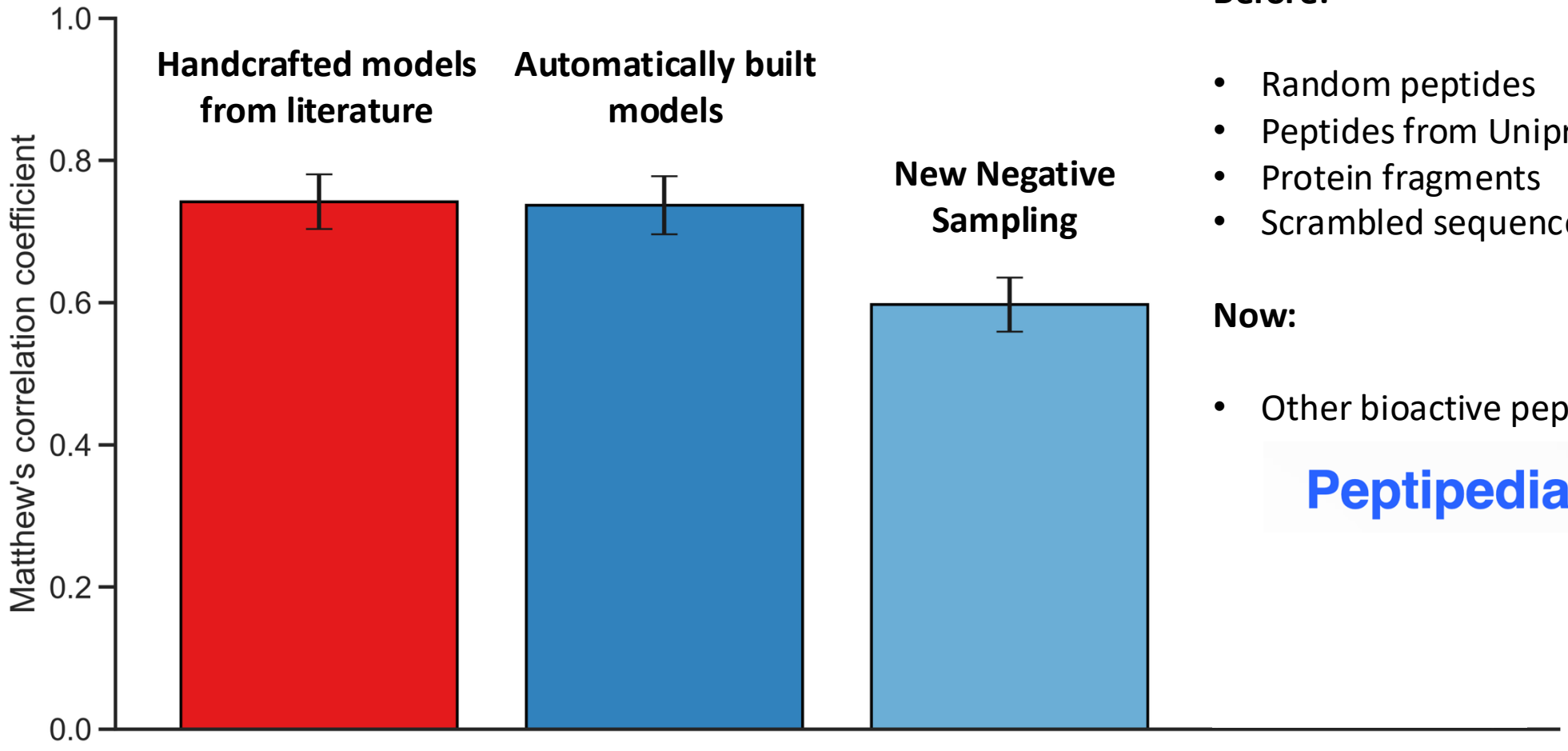

Before:

- Random peptides
- Peptides from Uniprot
- Protein fragments
- Scrambled sequences

Now:

- Other bioactive peptides

Peptipedia

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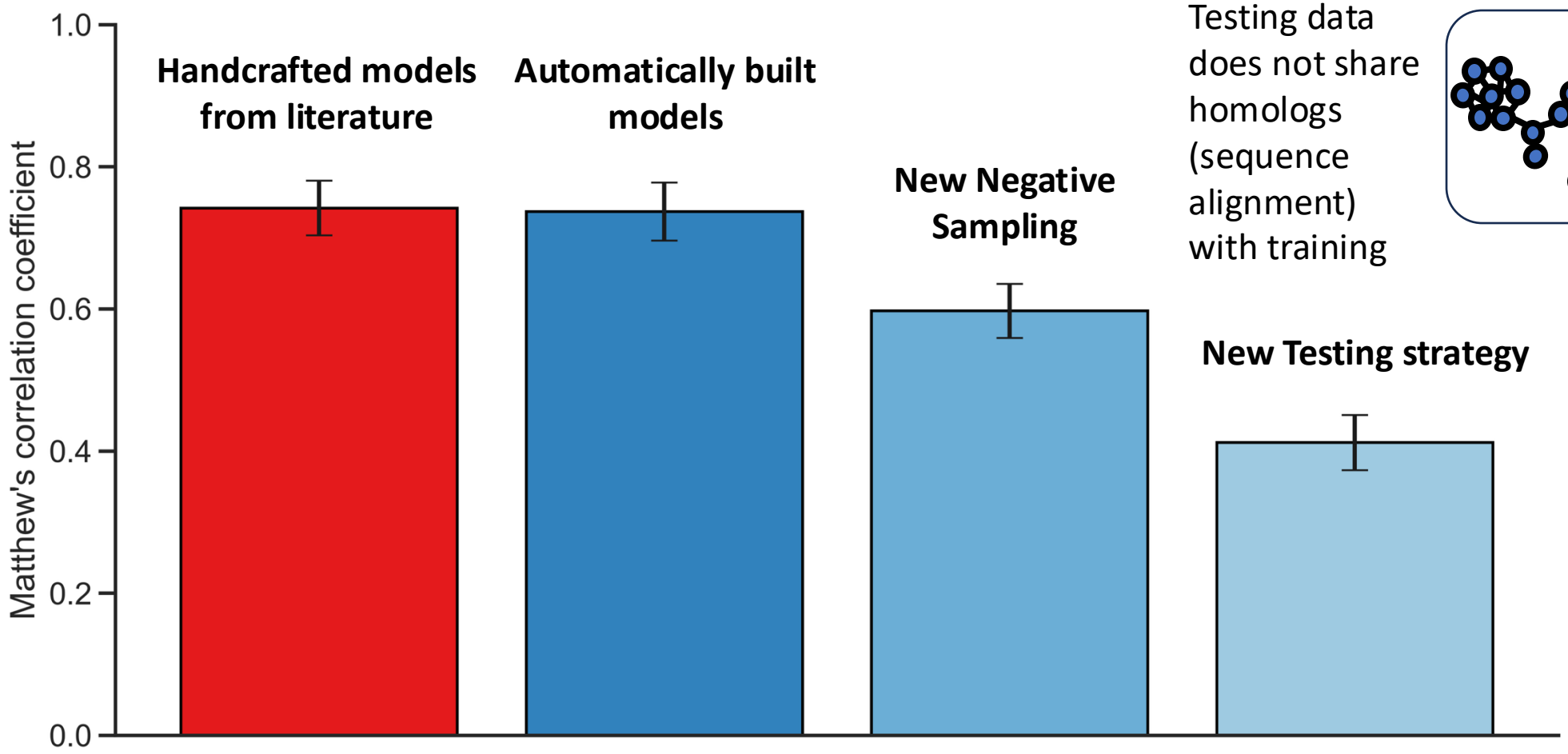

Testing data does not share homologs (sequence alignment) with training

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Webserver - GUI

AutoPeptideML

BIOINFORMATICS PUBLICATION CHEMRXIV PREPRINT GITHUB REPOSITORY DOCUMENTATION

Welcome to the AutoPeptideML webserver.

The next steps will help you build your own model.

0. Modelling task

First, start by defining the prediction task.

What is the prediction problem you are facing?

Classification (categorical values)

1. Inputs

In this section you will define the data from which you want the model to learn.

Download sample dataset

Please upload dataset with your peptides and their labels if available

Drag and drop file here
Limit 200MB per file
Browse files

CLI tool

```
--------------------------
| AutoPeptideML v.2.0.3  |
| By Raul Fernandez-Diaz |
--------------------------

Model builder


Part 1 - Define the data and preprocessing steps
[?] What is the modelling problem you're facing?:
  > Classification (returning categorical value)
    Regression(returnin continuous value)
```

Python Package

```python
df = pd.read_csv(osp.join(PATH, 'original_data', f'c-{dataset}.csv'))
apml = AutoPeptideML(
    data=df,
    outputdir=f'apml-{dataset}',
    sequence_field='SMILES',
    label_field='labels'
)
apml.build_models(
    task='class',
    reps=['esm2-8m', 'peptideclm', 'chemberta-2', 'ecfp-16'],
    models=['svm', 'knn', 'rf', 'lightgbm', 'xgboost'],
    device='mps',
    n_trials=10
)
apml.create_report()
return apml
```

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Automating ML for natural peptides - Conclusions

AutoPeptideML

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1. Automation achieves model performance on par with manually engineered previous studies
2. Proper automation leads to more robust model evaluation
3. Previous studied tended to overestimate model performance, due to:
   a) Negative sampling strategy
   b) Data leakage from similar peptides in training and testing

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Part 2 – Natural to synthetic peptides extrapolation

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Can we leverage data on cheaper experiments to prioritise more expensive experiments?

ChemRxiv™

Fernández-Díaz R, et al. How to build machine learning models able to extrapolate from standard to modified peptides. ChemRxiv. 2025; doi:10.26434/chemrxiv-2025-ggp8n-v3

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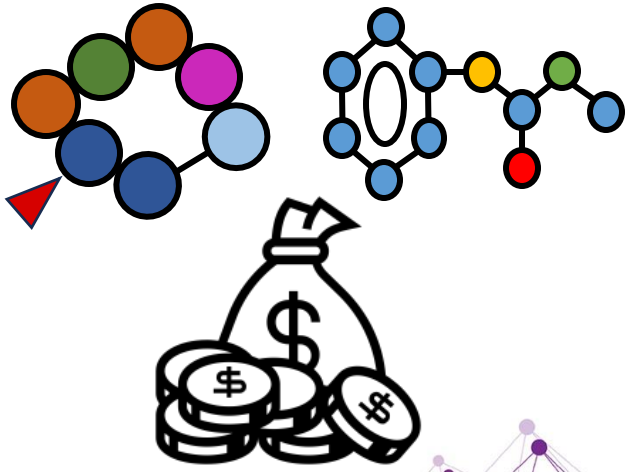

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Computational experiments

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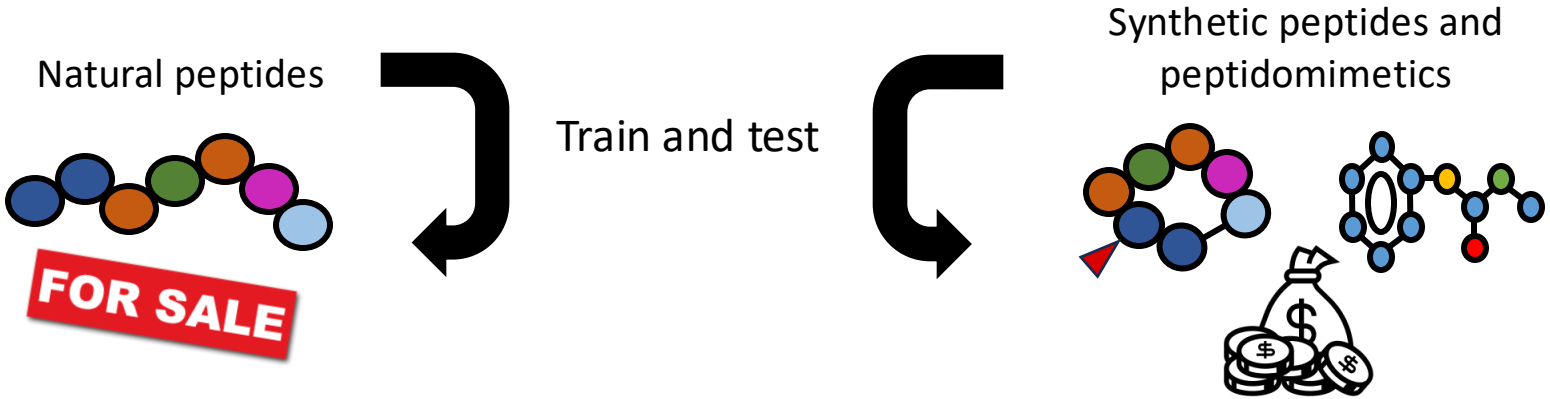
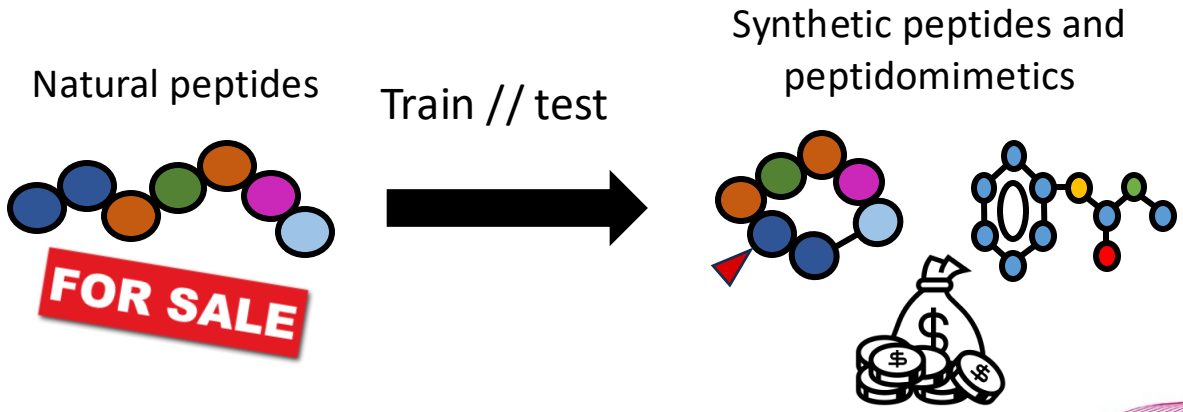
Interpolation



Extrapolation



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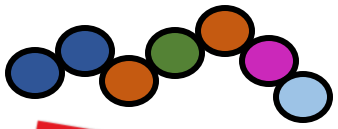
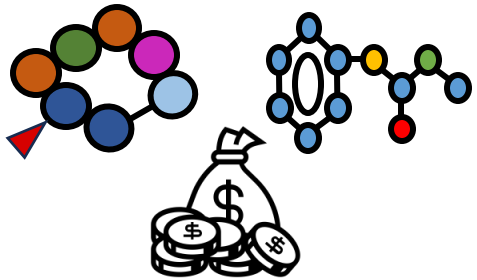
Interpolation

Natural peptides



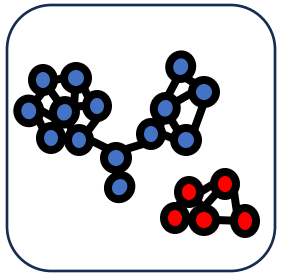
Train and test

Synthetic peptides and peptidomimetics



Small digression: Should we use sequence alignment for measuring peptide similarity?

Similarity-informed train/test split



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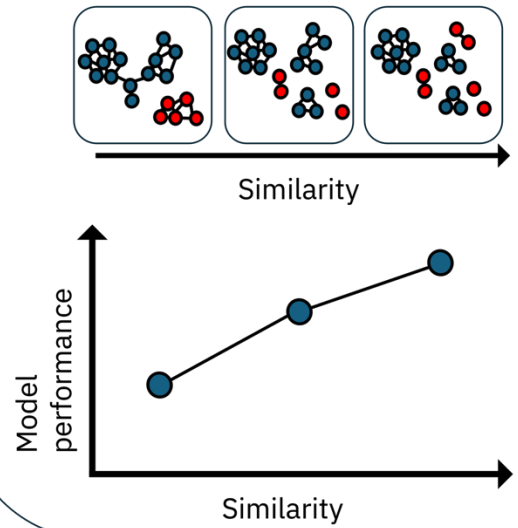
Finding the best similarity metric

Fernandez-Diaz R, et al. A new framework for evaluating model out-of-distribution generalisation for the biochemical domain. InThe Thirteenth International Conference on Learning Representations 2025.

Hestia-GOOD framework

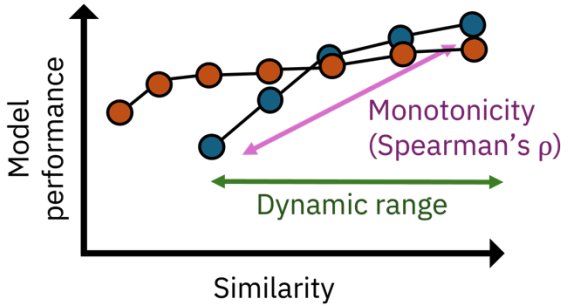
GOOD curve

Model performance as a function of train-test similarity



Similarity metric selection

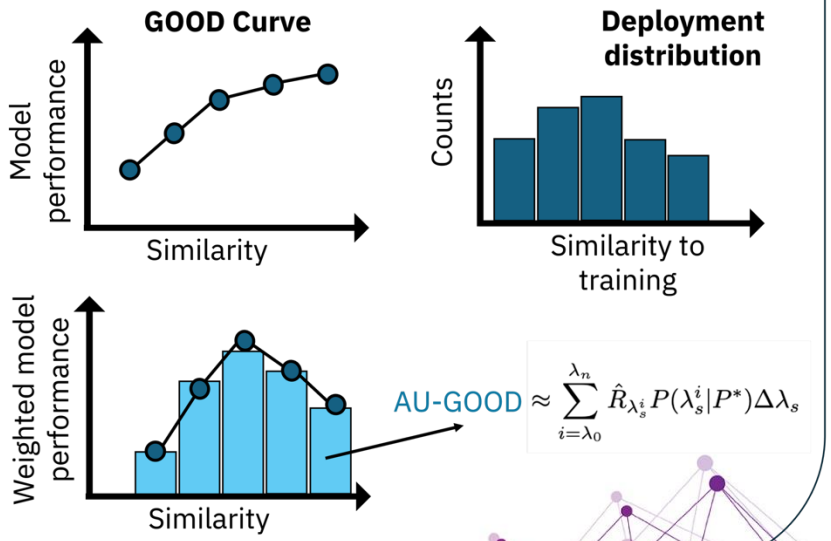
Quantitative analysis of best similarity function for a given task/dataset



- **Monotonicity:** Is model performance a function of train-test similarity?
- **Dynamic range:** What is the resolution of the similarity metric?

AU-GOOD metric

Estimation of model performance conditioned on a deployment distribution



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Best metrics for each dataset

ICLR 2025

Fernandez-Diaz R, et al. A new framework for evaluating model out-of-distribution generalisation for the biochemical domain. InThe Thirteenth International Conference on Learning Representations 2025.

- Analysis of **8** datasets:
  - 4 natural
  - 4 synthetic
- Chemical FPs are better than sequence alignment for natural peptides

Dataset	Peptide type	Task	Similarity Type	Similarity	Dynamic range (↑) [a]	Monotonicity (↑) [b]
Protein-peptide binding affinity	Standard	Regression	Chemical FP	MAPc-8	70 %	0.8 ± 0.1
Protein-peptide binding affinity	Modified	Regression	Chemical FP	MAPc-20	80 %	0.95 ± 0.03
Cell penetration	Standard	Classification	Chemical FP	MAPc-8	60 %	0.98 ± 0.04
Cell penetration	Modified	Classification	Chemical FP	MAPc-12	60 %	0.5 ± 0.2
Antibacterial	Standard	Classification	Chemical FP	MAPc-8	60 %	0.97 ± 0.02
Antibacterial	Modified	Classification	Chemical FP	ECFP-12	50 %	0.9 ± 0.1
Antiviral	Standard	Classification	Sequence Alignment	MMSeqs2	80 %	0.96 ± 0.05
Antiviral	Modified	Classification	Chemical FP	MAPc-12	70 %	0.6 ± 0.2

Metrics explored:

- ECFP various radii
- MAPc various radii
- MMSeqs2 (alignment)
- Needleman-Wunsch (alignment)
- ESM2-8M embedding distance
- Molformer-XL embedding distance

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Computational experiments

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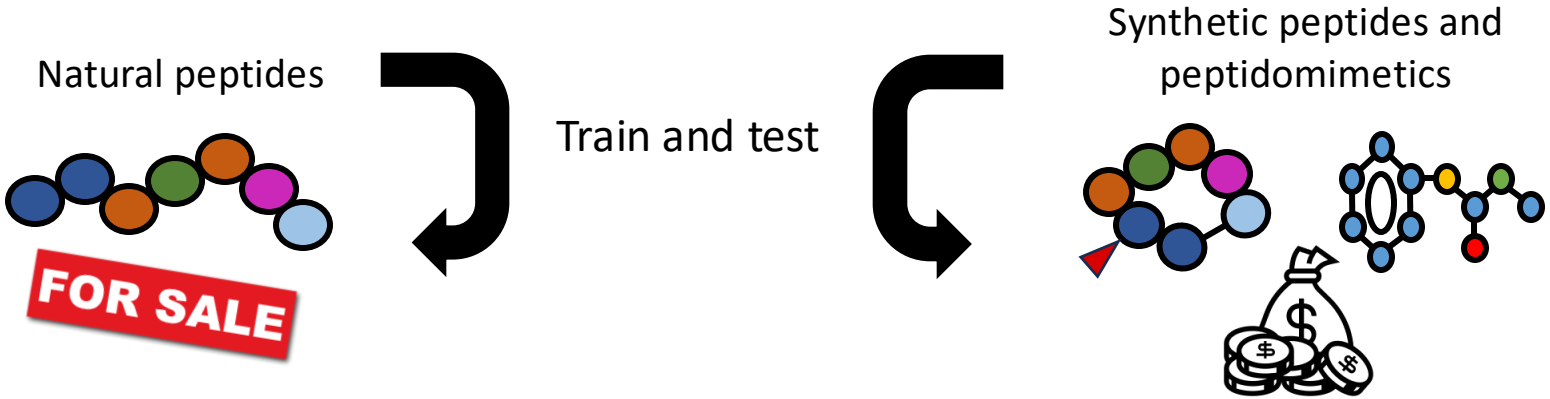

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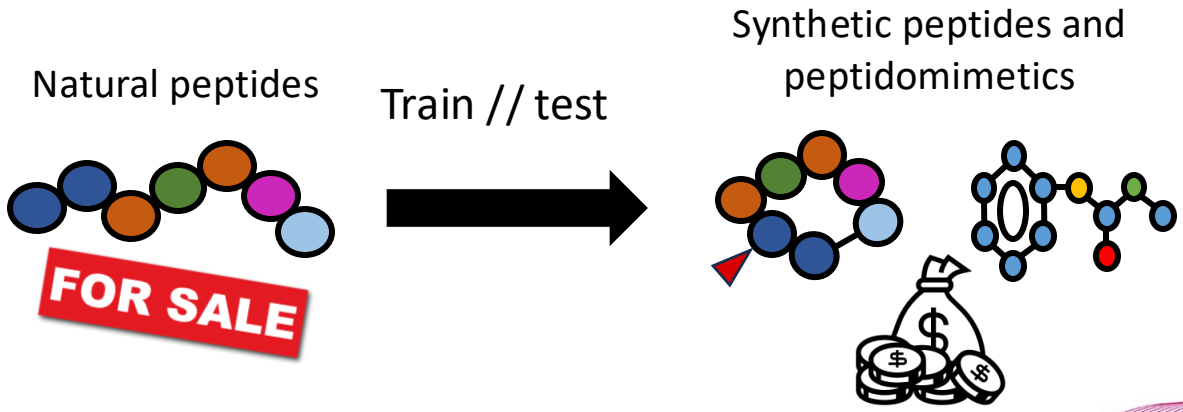

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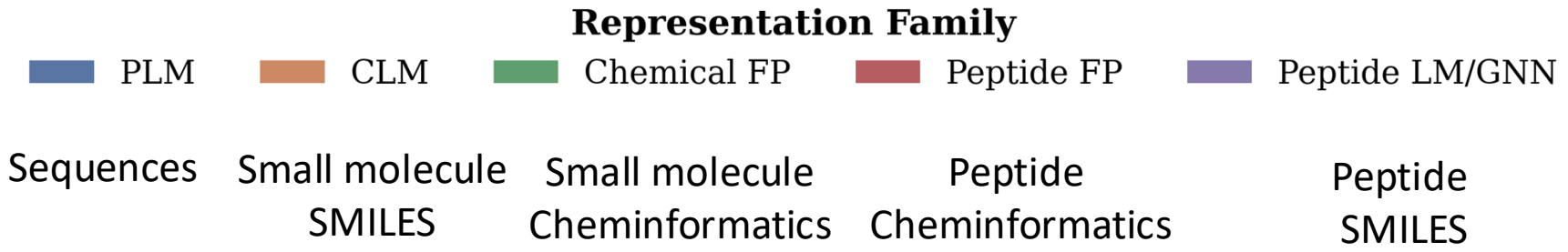
- Average on **4** datasets.
- Statistical analysis are Kruskal-Wallis with *post-hoc* Wilcoxon test.
- Significance defined with Bonferroni correction.



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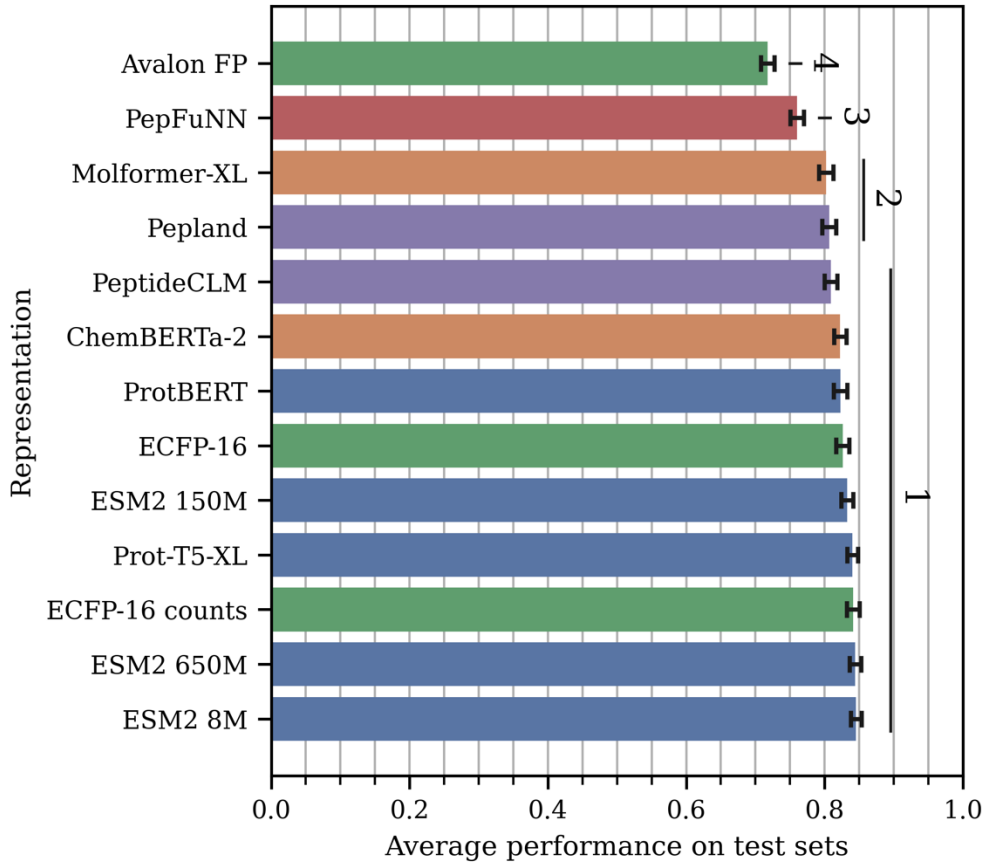
Natural to natural

Synthetic to synthetic



Representation Family

PLM | CLM | Chemical FP | Peptide FP | Peptide LM/GNN

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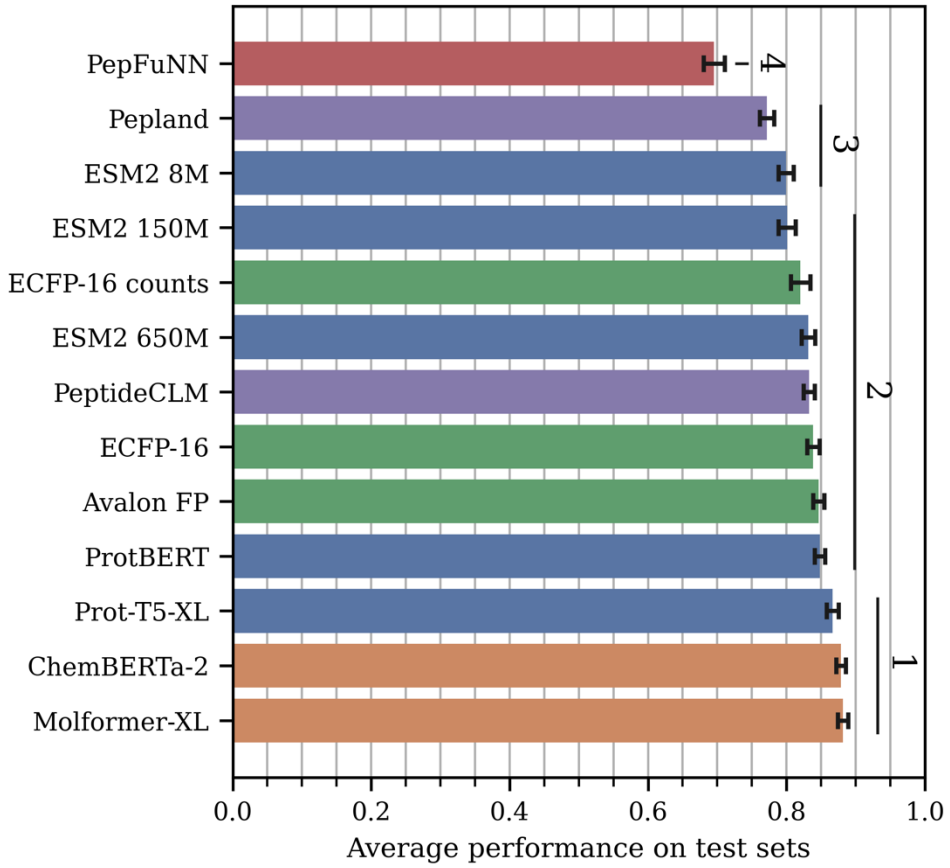

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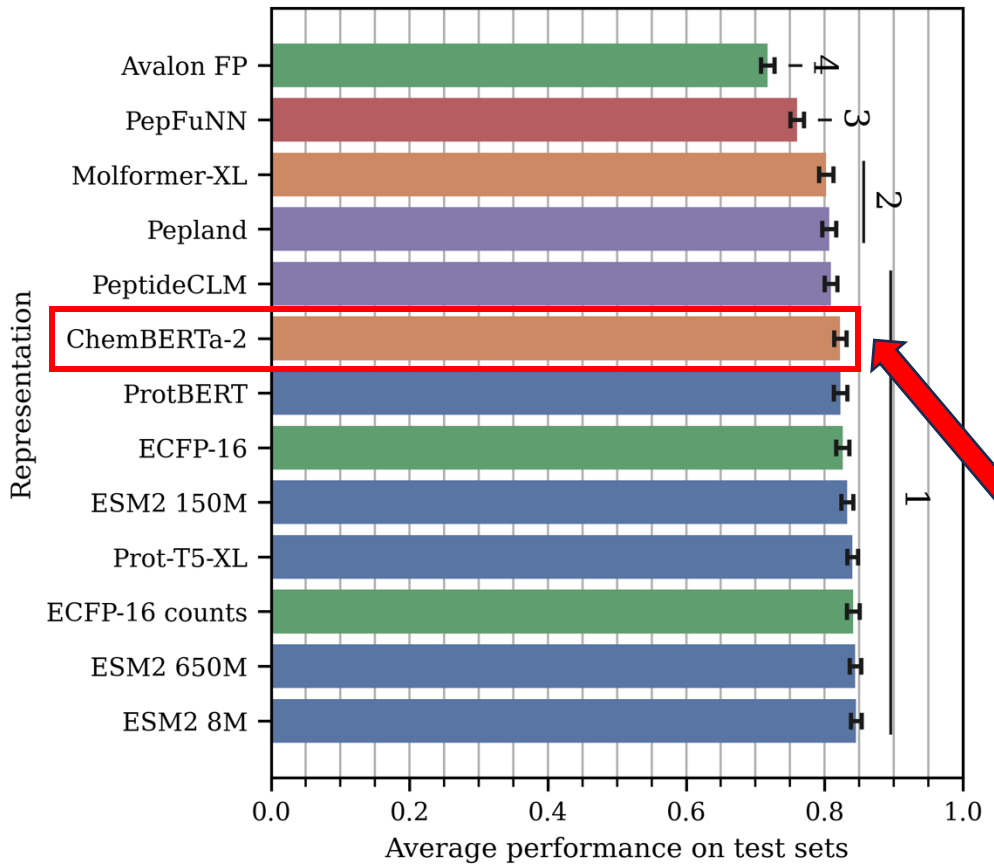

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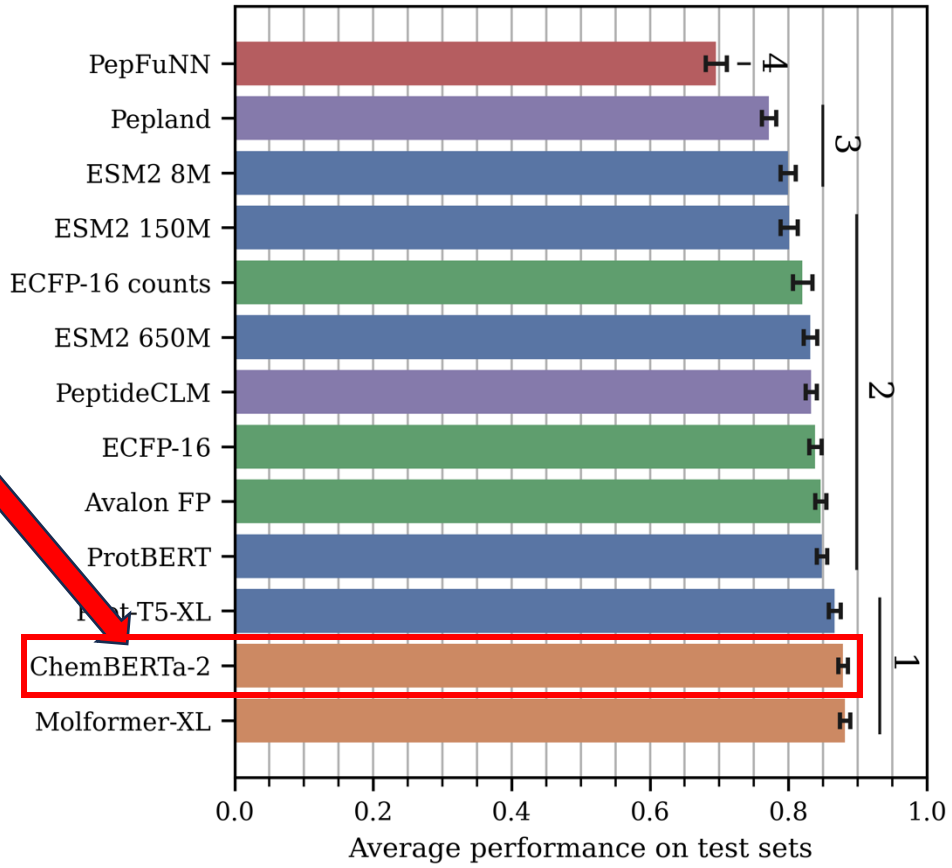

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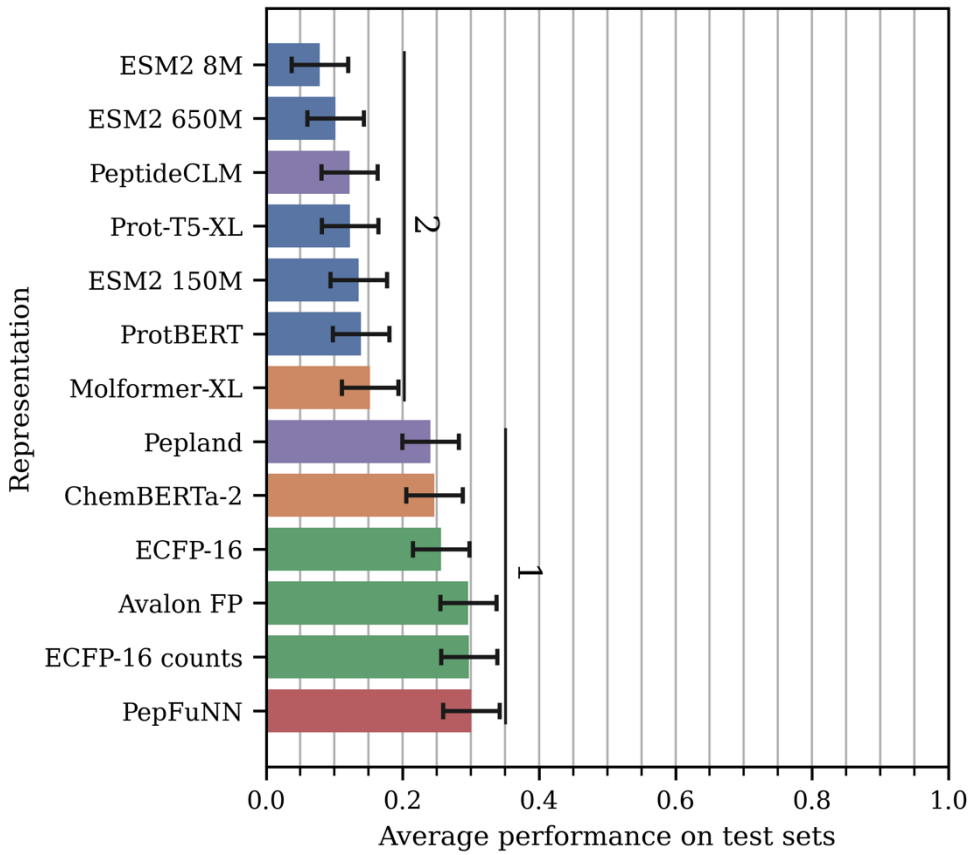
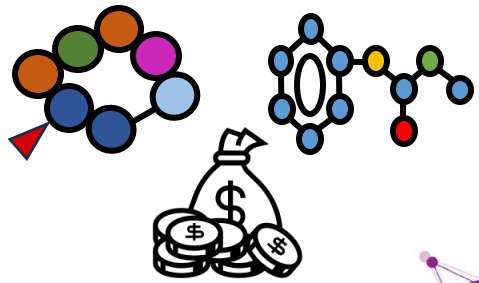


Natural peptides

Train // test

Synthetic peptides and peptidomimetics



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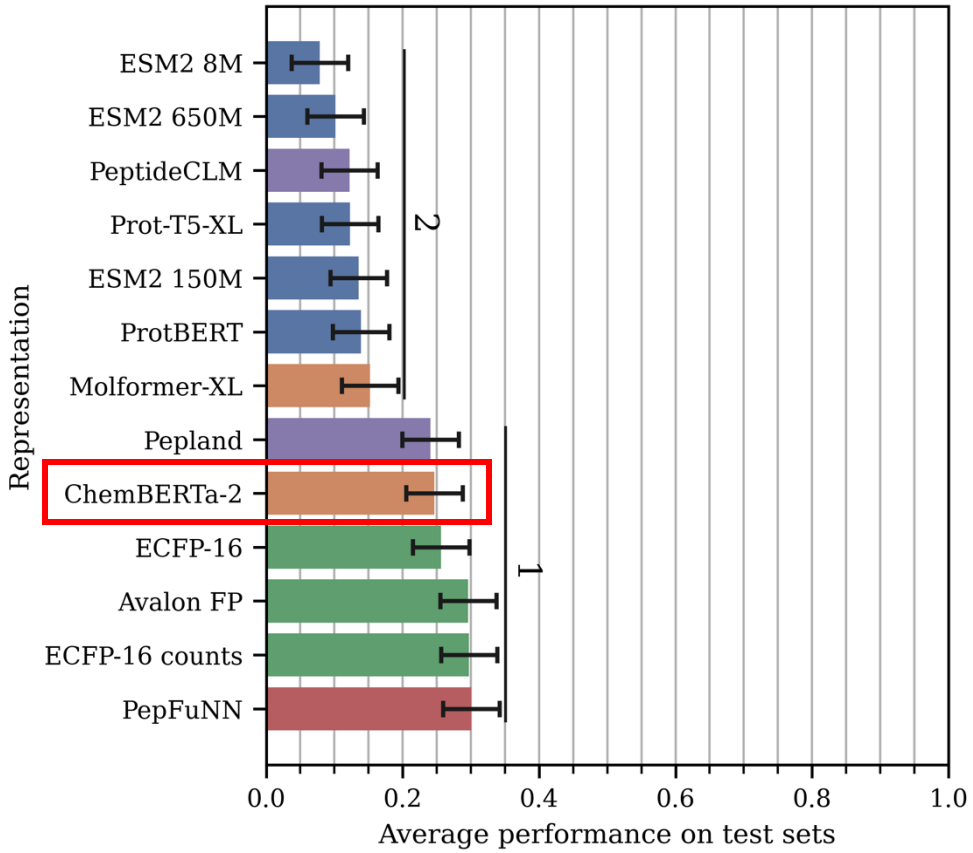

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Conclusions

1. Natural to synthetic extrapolation is possible, but models are less reliable
2. ChemBERTa-2 appears to be the most versatile tool to work with peptides
3. Chemical and Peptide Fingerprints are robust options as well

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Conclusions

1. AutoPeptideML **empowers** experimental scientist to build their own models
2. Dataset building (negative definition) and partitioning (train/test split) are key for proper model evaluation
3. Chemical fingerprints are better for partitioning natural and synthetic datasets than sequence alignment.
4. Natural to synthetic extrapolation is possible, but there is room for improvement
5. ChemBERTa-2 appears to be the most versatile tool, closely followed by chemical fingerprints

Contact info, papers, and slides of the presentation

More information and contact info

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Science Foundation Ireland sfi For what's next

UCD DUBLIN University College Dublin University for All

How to generalize machine learning models to both canonical and non-canonical peptides

Speaker: **Raúl Fernández-Díaz (PhD Candidate UCD – IBM Research)**

UCD: R. Cossio-Pérez, C. Agoni, D.C. Shields

IBM Research: T.L. Hoang, V. Lopez

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