Rethinking the generalization of drug target affinity prediction algorithms via similarity aware evaluation

Chenbin Zhang*, Zhiqiang Hu*, Chuchu Jiang*, Wen Chen, Jie Xu, Shaoting Zhang

Oral in 2025 at ICLR

29.04.2025

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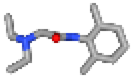
Background

1. The drug-target binding affinity prediction problem
2. Of the importance of proper data splitting
3. Issues with random splitting
4. SotA on fair predictive evaluation

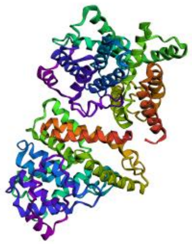
The drug-target binding affinity prediction problem screens drugs for interactions on a specific target.

e.g., **Protein docking** connect molecule and target and compute how strong the connection is

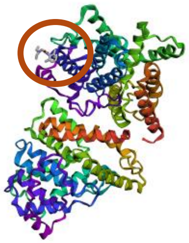
Drug
Lidocaine
cid:3676



Target (fixed)
PDE10A
pdb:4ajd



Predictive model
(e.g., MolModa **[1]**)



Docking score
-3.28 kcal/mol << 0

Other scores can be considered: KI or IC_{50}

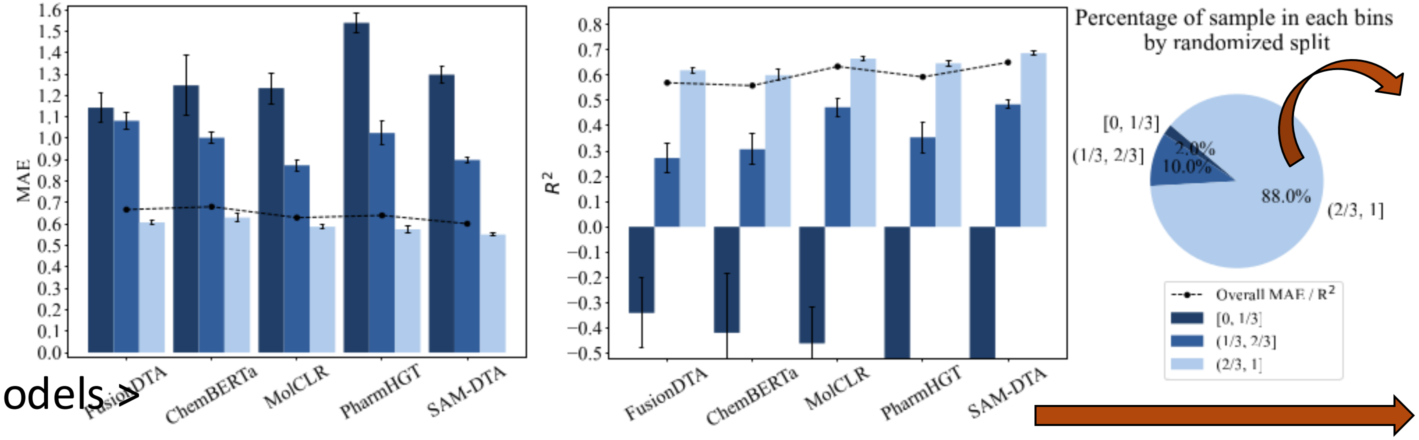
Binding is (often) an inhibitory action

- A prefiltering task in drug discovery / repurposing
- Lots of literature (structure-based, sequence-based, similarity-based, …)

A classifier can be trained with text or tabular data, and evaluated on R^2 or MSE metrics

[1] Kochnev, … & Durrant. (2024). MolModa: accessible and secure molecular docking in a web browser. *Nucleic Acids Research*, *52*(W1), W498-W506. *https://durrantlab.pitt.edu/molmoda/#*

Of the importance of proper data splitting related to fair evaluation of model generalizability.

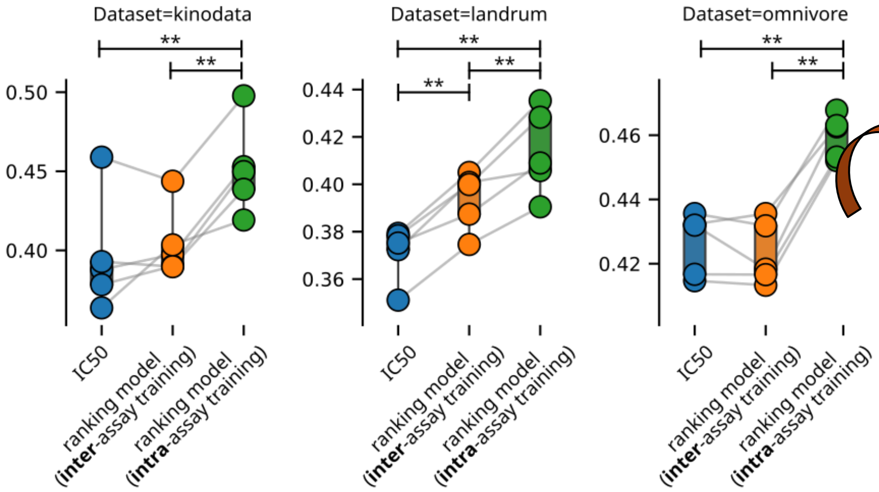


Models ->

From Fig. 1 in the paper.

Most drugs in the test set are **similar** to drugs in the train set

Driving the *seemingly* good performance on the test set (≈ data leakage)



Drugs often cluster by assay origin
Might lead to less efficient training due to batch effect and unfair comparisons

Aggregated assay-wise evaluation and training

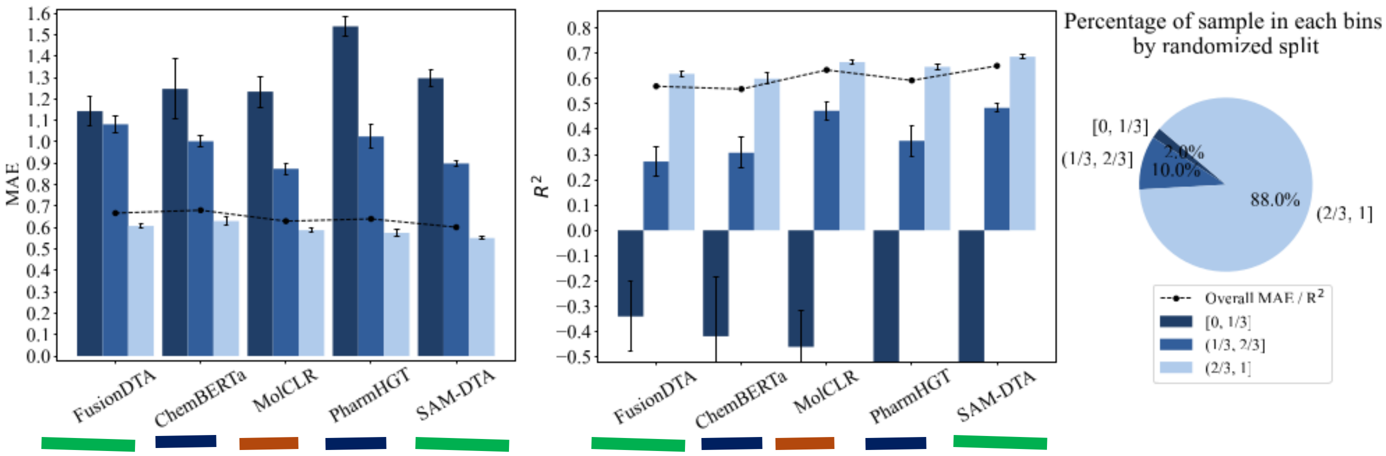
From Fig. 4 in Backenköhler et al. (2025). Assay-Based Machine Learning: Rethinking Evaluation in Drug Discovery. *ChemRxiv*.

Issues with random splitting and why and when random splitting can be applied.

Random splitting "balances out" the sample similarity between the train/test sets
if the samples are **drawn iid = strong assumption which does not hold for drugs (too optimistic)**

Tested drugs:

- Different exposure times and doses but same molecule
- Some drugs are more common (with potentially similar mechanisms of action) e.g., cancer
- Assay-related batch effect
- Relatively small data sets (< 5k drugs per target in open data sets)



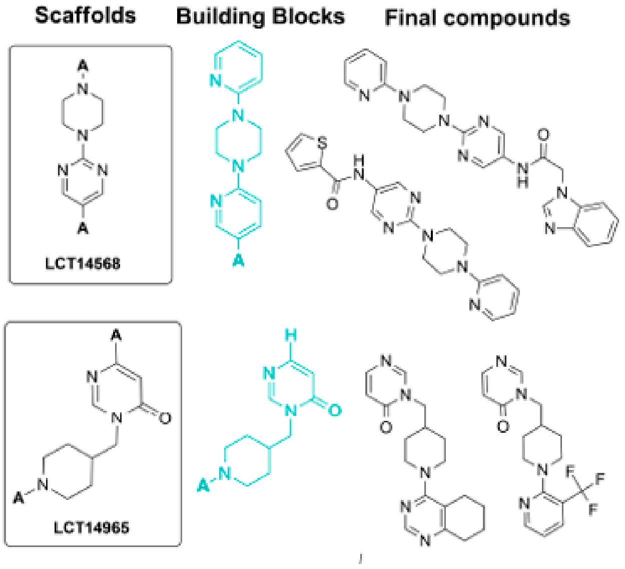
From Fig. 1 in the paper.

Observations still stand for other data sets, drug features, predictive models, evaluation metrics and similarity measures

- 🟧 GCN on atom graphs
- 🟩 NNs on fingerprints
- 🟦 Transformers

Fair predictive evaluation in SotA alternatives to random splitting in related works.

Scaffold splitting = identify (e.g., Markush, Murcko **[2]**) scaffolds and segregate molecules with the same scaffolds (≈ in the same structural class) in the train or test sets



Adapted from **[3]**

Pros

Scaffolds are a quick way to assess the structural similarity between drugs

Cons **[4]**

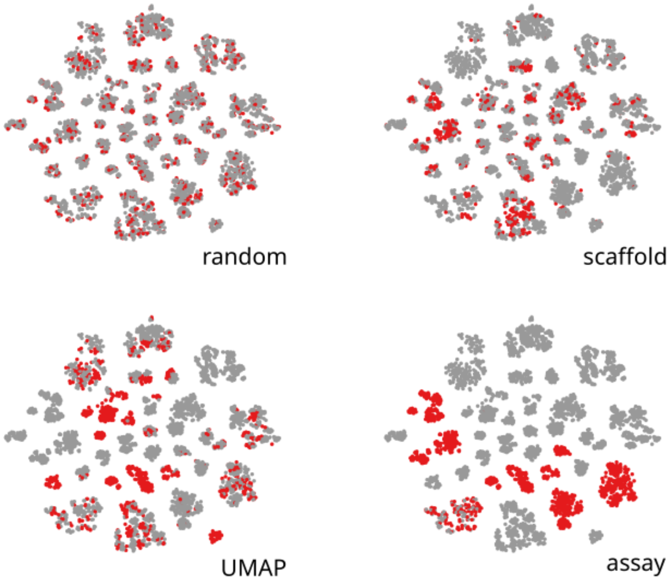
No standard scaffold-finding algorithm

Scaffolds are not necessarily relevant to the mechanism of action

[2] Bemis, & Murcko. (1996). The properties of known drugs. 1. Molecular frameworks. *Journal of medicinal chemistry*, *39*(15), 2887-2893.
[3] *https://lifechemicals.com/screening-libraries/scaffolds-and-scaffold-based-compounds*
[4] *https://greglandrum.github.io/rdkit-blog/posts/2024-05-31-scaffold-splits-and-murcko-scaffolds1.html*

Fair predictive evaluation in SotA alternatives to random splitting in related works.

Similarity splitting = identify similarity groups of drugs (e.g., Taylor-Butina clustering, UMAP **[5]** or stratification **[6]** on features) and segregate same-group molecules in the train or test sets



T-SNE map of drugs **[7]**. 🔴 test ● train

Pros

Seems to be fairer than scaffold splits **[5]**

Cons

No standard dimension-reduction / clustering

No control on the distribution of similarities in the train and test set

[5] Guo, … & Ballester . (2024, September). Scaffold Splits Overestimate Virtual Screening Performance. In *International Conference on Artificial Neural Networks* (pp. 58-72). Cham: Springer Nature Switzerland.
[6] Farias, … & Bastos-Filho. (2020). Similarity Based Stratified Splitting: an approach to train better classifiers. *ArXiv*.
[7] Backenköhler et al. (2025). Assay-Based Machine Learning: Rethinking Evaluation in Drug Discovery. *ChemRxiv*.

Fair predictive evaluation in SotA alternatives to random splitting in related works.

SIMPD **[8]** = use a multi-objective genetic algorithm to mimic time-based-splitting, where assays produced within the same time frame are grouped together

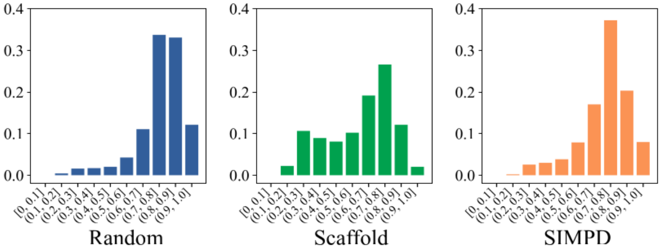
Candidate: Cluster drugs and assign clusters to train/test at random until |test| is 20% of all data
Fitness: Chemical requirements (e.g., median #heavy atoms)
Criteria: For train and test
Entropy < 0.9 x log2(#clusters)

- At each iteration, recombine the fittest candidates to produce new solutions
- Stop when a solution fits the criteria

Pros **[8]**

Less pessimistic than similarity-based splits

Cons



Adapted from **Fig. 4** in the paper. Sample similarity histograms b/w train and test sets.

Sometimes produces the same similarity distribution as random

[8] Landrum, ... & Riniker. (2023). SIMPD: an algorithm for generating simulated time splits for validating machine learning approaches. *Journal of cheminformatics*, *15*(1), 119.

Content of the paper

"SAE [...] a framework of **similarity aware evaluation** in which a novel split methodology is proposed to adapt to any desired distribution"

Objectives:

- Split drugs into train / test subsets according to their similarity
- "Controllable" and tractable approach even for larger data sets

Competitive advantages wrt SotA:

- Target similarity distribution is often uniform but SAE can reproduce the distribution in an external test set

Content of the paper

"SAE [...] a framework of **similarity aware evaluation** in which a novel split methodology is proposed to adapt to any desired distribution"

1. Target optimization problem
2. Tractable optimization algorithm for data splitting
3. Experimental results

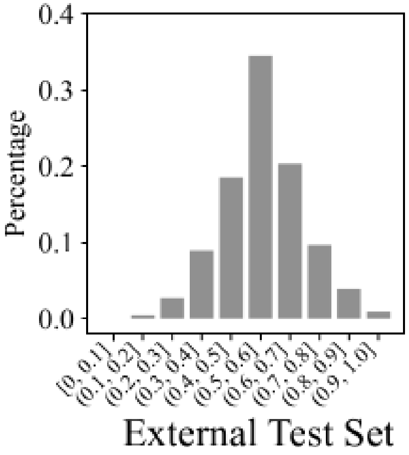
Target optimization problem find a test subset of size αN matching a target sample similarity histogram.

K = #similarity bins
N = #drugs in total

o^c_k = #drugs i with c_i=1 and in bin k

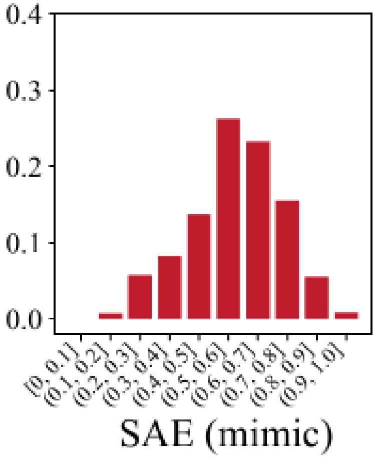
e_k = target %drugs in bin k
e.g., balanced would yield $e_k = 1/K$

Fig. 4 in paper.



$$\min_{\substack{\mathbf{c}\in\{0,1\}^N \\ |\mathbf{c}|^{1}=[\alpha N]}} \quad f(\mathbf{c}) = \sum_{k<K} (o^{\mathbf{c}}_k - \alpha N e_k)^2 \,/\, (\alpha N e_k)$$

< max similarity with training samples for each test sample



1. Compute $(e_k)_k$ from target histogram

2. Solve the minimization problem in **c**

3. Use the elements associated with 1's in **c** as testing subset

f(c) looks like the Pearson χ^2 statistic with K-1 degrees of freedom

Target optimization problem find a test subset of size αN matching a target sample similarity histogram.

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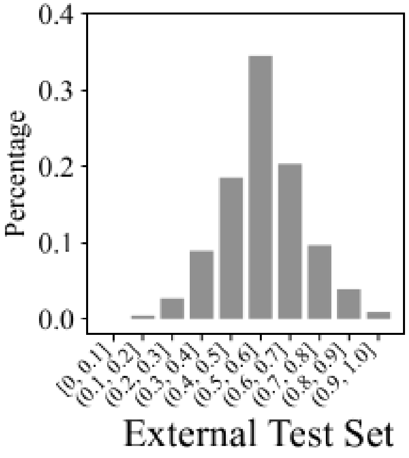

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$|\{\ i \mid c_i=1$ and $\max_{cj=0} \mathrm{sim}(i,j) \in [\mathrm{bin}_{k-1}, \mathrm{bin}_k]\ \}|$

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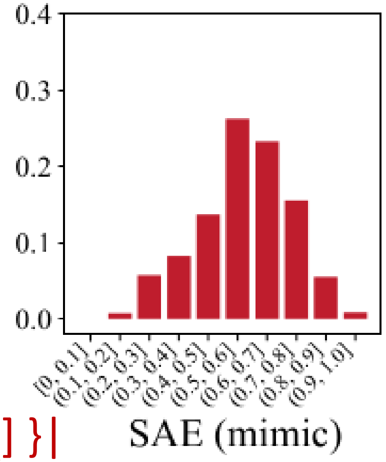
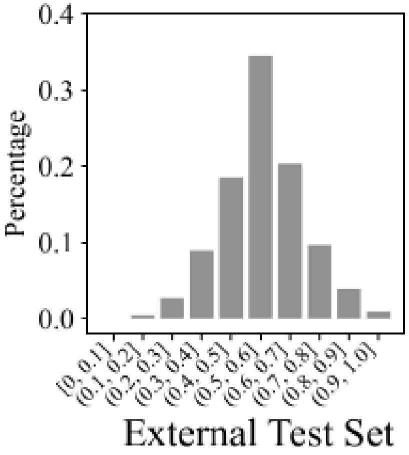


1. Compute $(e_k)_k$ from target histogram
2. ~~Solve the minimization problem in **c**~~
3. Use the elements associated with 1's in **c** as testing subset

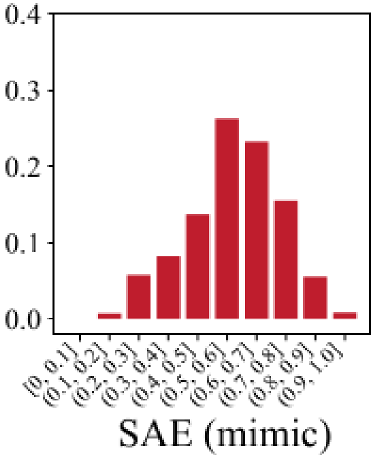
Tractable optimization algorithm for data splitting relax the problem to avoid integer prog and non-diff functions.

K = #similarity bins
N = #drugs in total



$$\min_{\substack{\mathbf{w}\in[0,1]^N \\ |\mathbf{w}|^1=[\alpha N]}} \quad f(\mathbf{w}) = \sum_{k<K} (o^{\mathbf{w}}_k - \alpha N e_k)^2 / (\alpha N e_k) + \lambda \ell_{\text{entropy}}(\mathbf{w})$$

Fig. 4 in paper.



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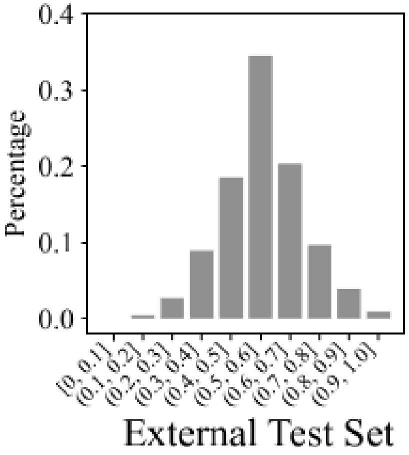

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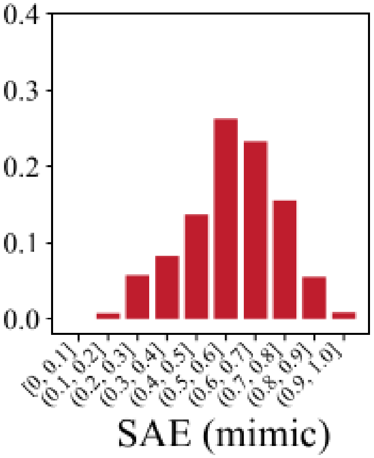
$$\approx |\{\, i \mid c_i=1 \text{ and } \max_{c_j=0} \text{sim}(i,j) \in [\text{bin}_{k-1}, \text{bin}_k] \,\}|$$



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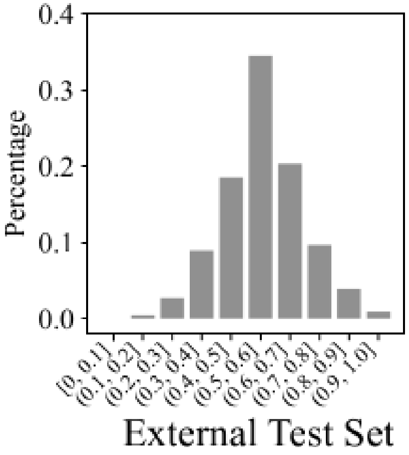

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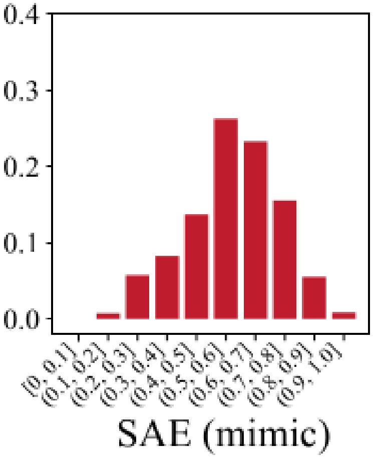

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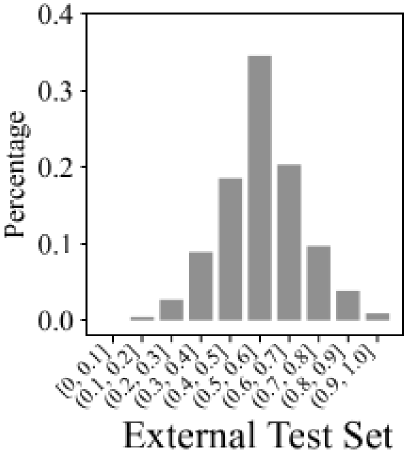

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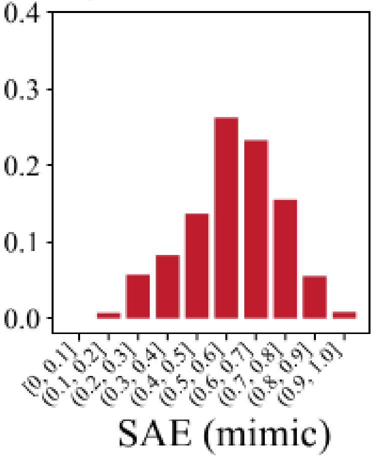
$$+ \lambda \ell_{entropy}(\mathbf{w})$$

Fig. 4 in paper.



$\approx |\{ i \mid c_i=1 \text{ and } \max_{cj=0} \text{sim}(i,j) \in [bin_{k-1}, bin_k] \}|$

$\approx \sum_{i<N} w_i \, I(\max_{cj=0} \text{sim}(i,j) \in [bin_{k-1}, bin_k])$

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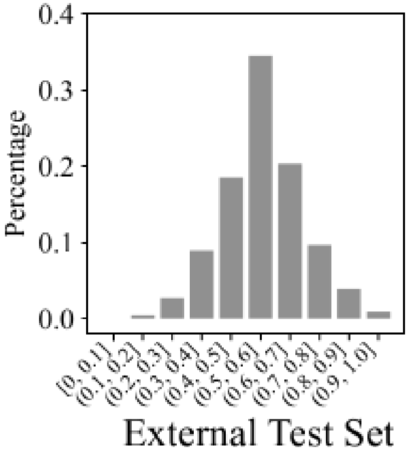

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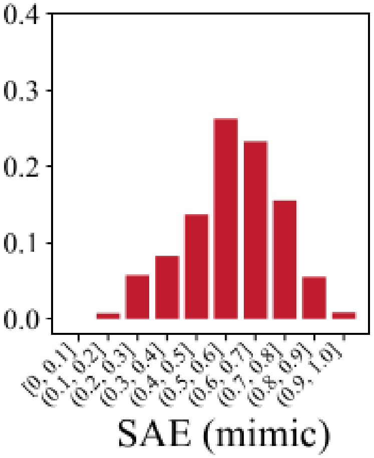

$$\approx |\{ i \mid c_i=1 \text{ and } \max_{cj=0} \operatorname{sim}(i,j) \in [\text{bin}_{k-1}, \text{bin}_k] \}|$$

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$$\approx \sum_{i<N} w_i \, I(\operatorname{LogSumExp}((1-\mathbf{w}) \text{ x } \mathbf{sim(i,.)}) \in [\text{bin}_{k-1}, \text{bin}_k])$$

$$\operatorname{LogSumExp}(\boldsymbol{x}) = \beta^{-1} \log\Big(\sum_{i<N} \exp(\beta x_i)\Big)$$
= multivariate SoftPlus

$$\max_i x_i \leq \operatorname{LogSumExp}(\boldsymbol{x}) \leq \max_i x_i + \underbrace{\log(N)/\beta}_{\text{Controls the accuracy}}$$

Tractable optimization algorithm for data splitting relax the problem to avoid integer prog and non-diff functions.

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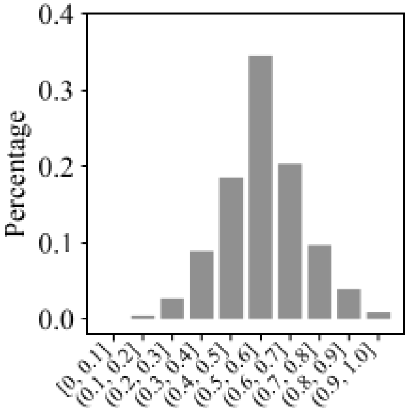
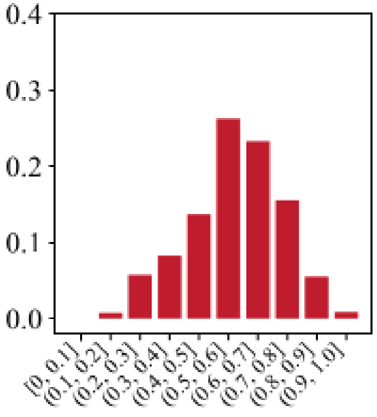


External Test Set

$$\min_{\substack{\mathbf{w}\in[0,1]^N \\ |\mathbf{w}|^1=[\alpha N]}} \quad f(\mathbf{w}) = \sum_{k<K} (o^{\mathbf{w}}_k - \alpha N e_k)^2 / (\alpha N e_k) + \lambda \ell_{\text{entropy}}(\mathbf{w})$$

Fig. 4 in paper.



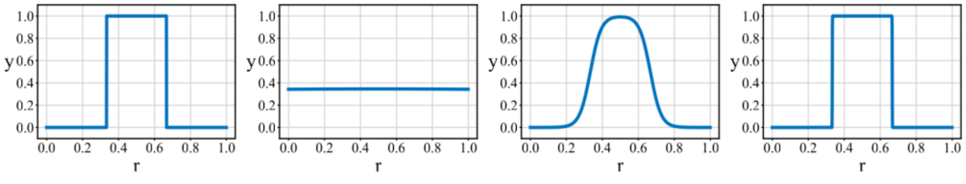
SAE (mimic)

$$\approx |\{ i \mid c_i=1 \text{ and } \max_{c_j=0} \text{sim}(i,j) \in [\text{bin}_{k-1}, \text{bin}_k] \}|$$

$$\approx \sum_{i<N} w_i \, \mathbb{I}(\max_{c_j=0} \text{sim}(i,j) \in [\text{bin}_{k-1}, \text{bin}_k])$$

$$\approx \sum_{i<N} w_i \, \mathbb{I}(\max_j (1-w_j)\text{sim}(i,j) \in [\text{bin}_{k-1}, \text{bin}_k])$$

$$\approx \sum_{i<N} w_i \, \mathbb{I}(\underbrace{\text{LogSumExp}\big((1-\mathbf{w}) \times \textbf{sim(i,.)}\big)}_{= r_i} \in [\text{bin}_{k-1}, \text{bin}_k])$$



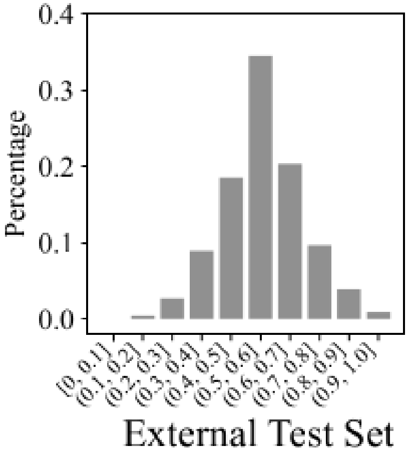
(a) $\mathbb{I}(\frac{1}{3} < r \leq \frac{2}{3})$ (b) $\sigma = 1$ (c) $\sigma = 0.1$ (d) $\sigma = 0.01$

Assume Prob($r_i \in [\text{bin}_{k-1}, \text{bin}_k]$) = Norm($r_i$; c_k, σ_k) where $c_k = (\text{bin}_k + \text{bin}_{k-1})/2$ is the center of the bin and σ_k controls the accuracy

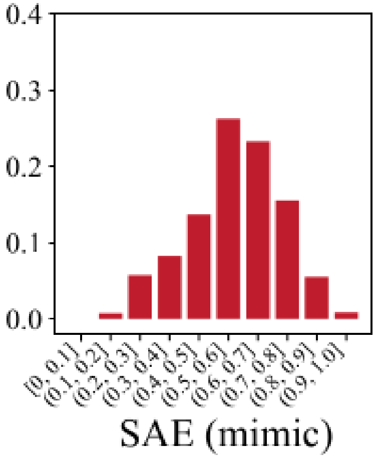
Tractable optimization algorithm for data splitting relax the problem to avoid integer prog and non-diff functions.

K = #similarity bins
N = #drugs in total

Fig. 4 in paper.



$$\min_{\substack{\mathbf{w}\in[0,1]^N \\ |\mathbf{w}|^1=[\alpha N]}} \quad f(\mathbf{w}) = \sum_{k<K} (o^{\mathbf{w}}_k - \alpha N e_k)^2 / (\alpha N e_k) + \lambda \ell_{entropy}(\mathbf{w})$$



$$\approx |\{ i \mid c_i=1 \text{ and } \max_{c_j=0} sim(i,j) \in [bin_{k-1}, bin_k] \}|$$

$$\approx \sum_{i<N} w_i \, I(\max_{c_j=0} sim(i,j) \in [bin_{k-1}, bin_k])$$

$$\approx \sum_{i<N} w_i \, I(\max_j (1-w_j) sim(i,j) \in [bin_{k-1}, bin_k])$$

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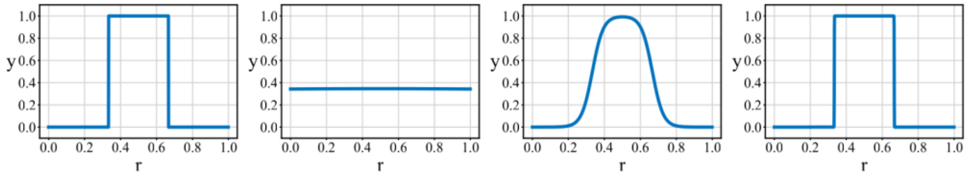


$(a)\ \mathbb{I}(\frac{1}{3} < r \leq \frac{2}{3})$ $(b)\ \sigma = 1$ $(c)\ \sigma = 0.1$ $(d)\ \sigma = 0.01$

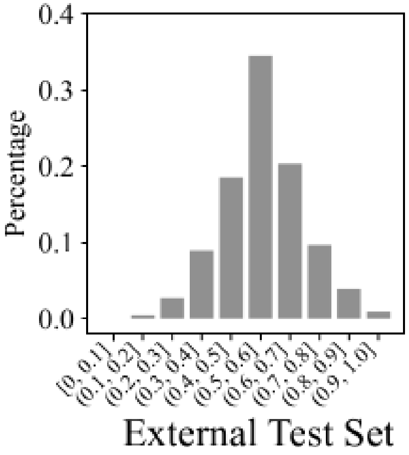
Assume $\text{Prob}(r_i \in [bin_{k-1}, bin_k]) = \text{Norm}(r_i ; c_k, \sigma_k)$
where $c_k = (bin_k + bin_{k-1})/2$ is the center of the bin
and σ_k controls the accuracy

$$\propto \sum_{i<N} w_i \, \text{Norm}(r_i ; c_k, \sigma_k)$$

Tractable optimization algorithm for data splitting relax the problem to avoid integer prog and non-diff functions.

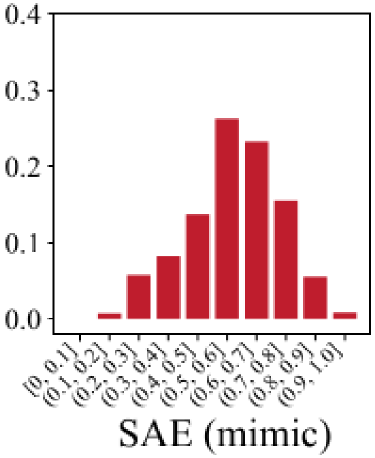
K = #similarity bins
N = #drugs in total

e_k = target %drugs in bin k
e.g., balanced would yield $e_k = 1/K$ Fig. 4 in paper.



$$\min_{\substack{\mathbf{w}\in[0,1]^N \\ |w|^1=[\alpha N]}} f(\mathbf{w}) = \sum_{k<K} (o^{\mathbf{w}}_k - \alpha N e_k)^2 / (\alpha N e_k) + \lambda \ell_{\text{entropy}}(\mathbf{w})$$

$$\propto \sum_{i<N} w_i \,\text{Norm}(r_i\,;\, c_k, \sigma_k)$$

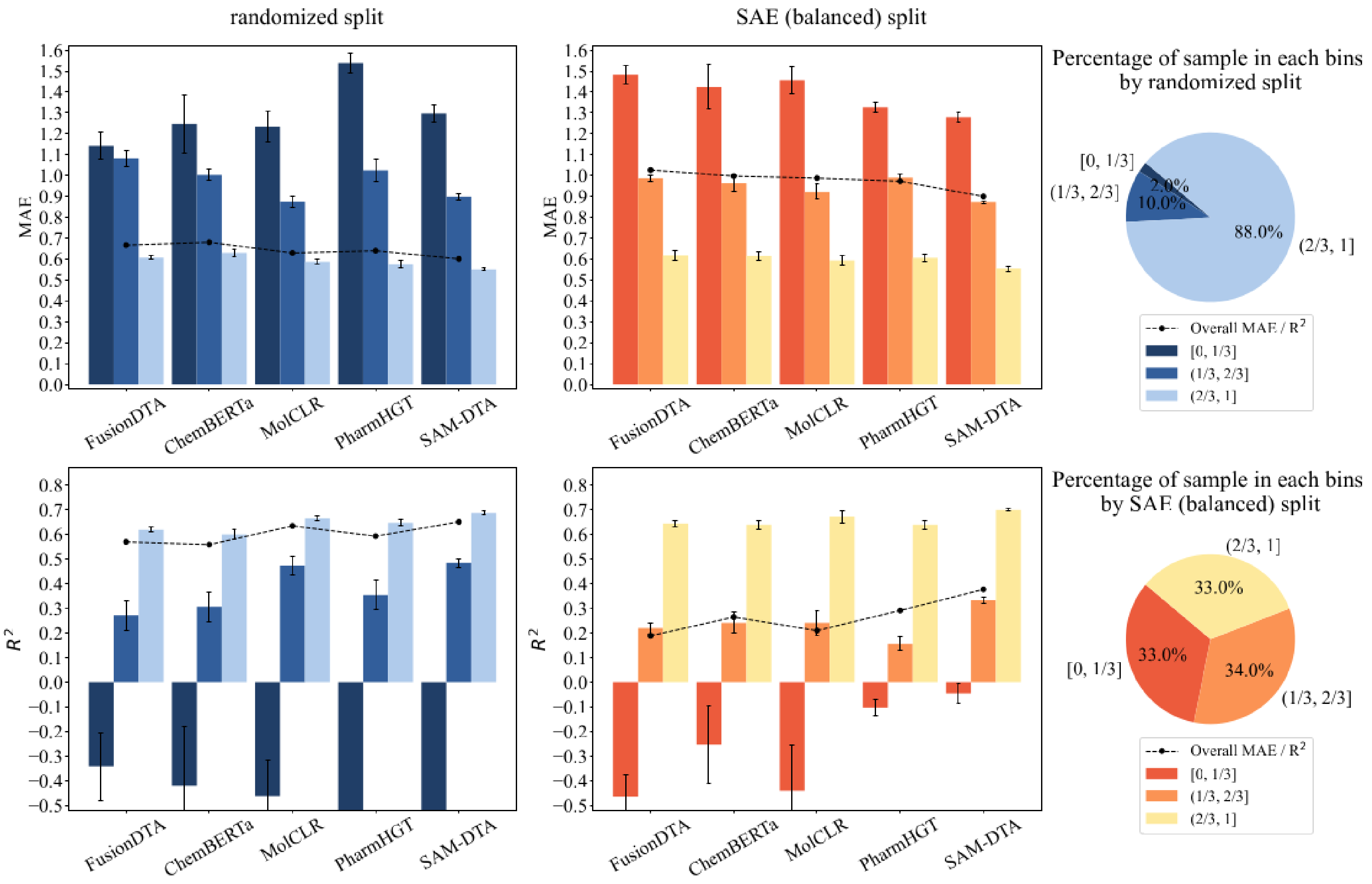


1. Compute $(e_k)_k$ from target histogram

2. Solve the minimization problem in **w** with standard numerical approaches for convex optimization

3. Use the elements associated with 1's in **w** as testing subset

Experimental results Fairer evaluation and balanced similarity between the train and test subsets.

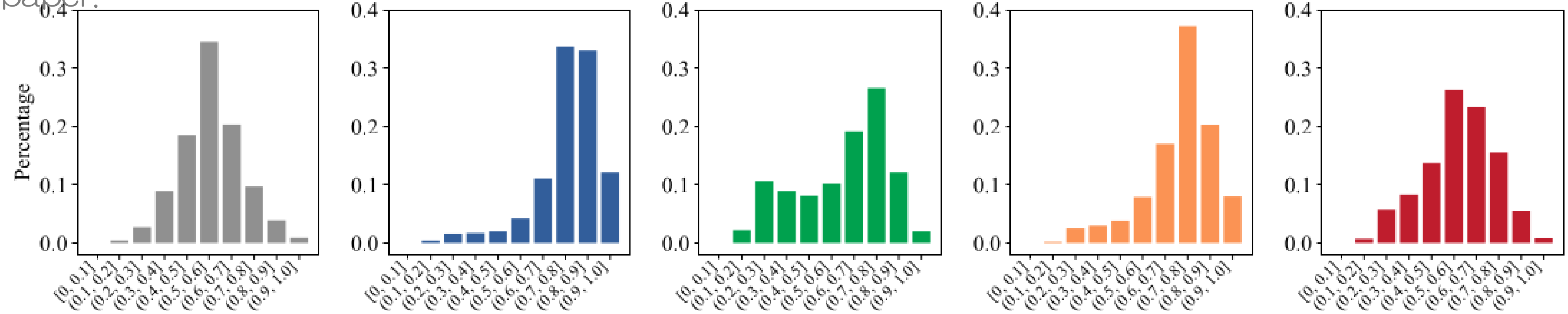


for all bin k, e_k=1/K

Fig. 1 in the paper.

Experimental results Reproduce similar conditions as in a target testing subset or condition ("any distribution").

Fig. 4 in the paper.



(a) External Test Set

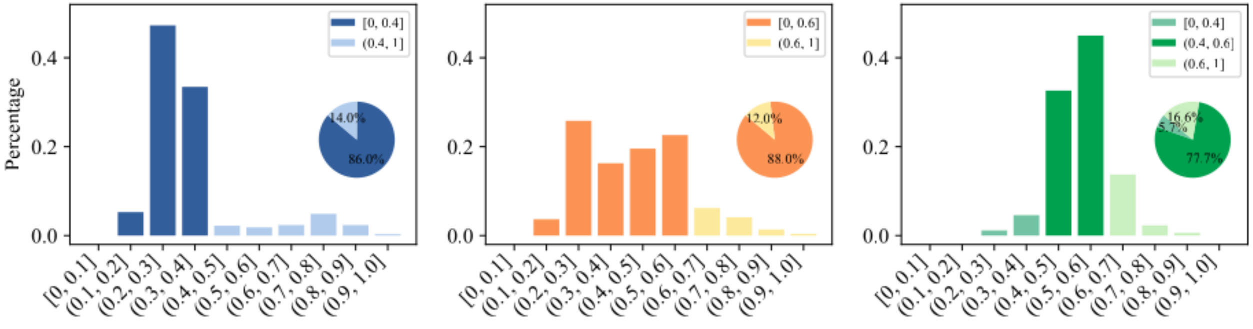
(b) Random

(c) Scaffold

(d) SIMPD

(e) SAE (mimic)

Custom $(e_k)_k$ from target histogram



(a) Test data distribution with 0~0.4 split

(b) Test data distribution with 0~0.6 split

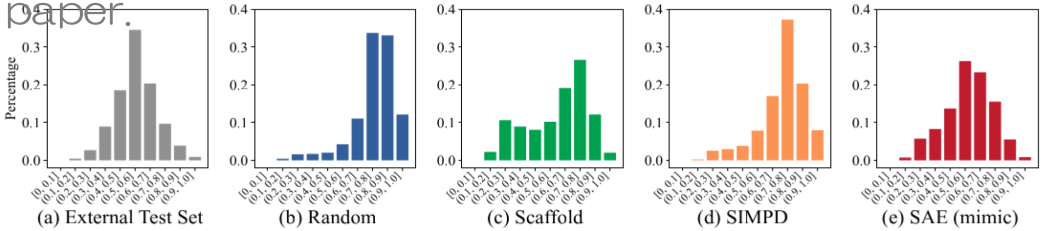
(c) Test data distribution with 0.4~0.6 split

Constraint the range of train-test sample similarities

Fig. 6 in the paper.

Experimental results Reproduce similar conditions as in a target testing subset or condition ("any distribution").

Fig. 4 in the paper.



(a) External Test Set (b) Random (c) Scaffold (d) SIMPD (e) SAE (mimic)

Custom $(e_k)_k$ from target histogram

More reproducible performance on external test sets

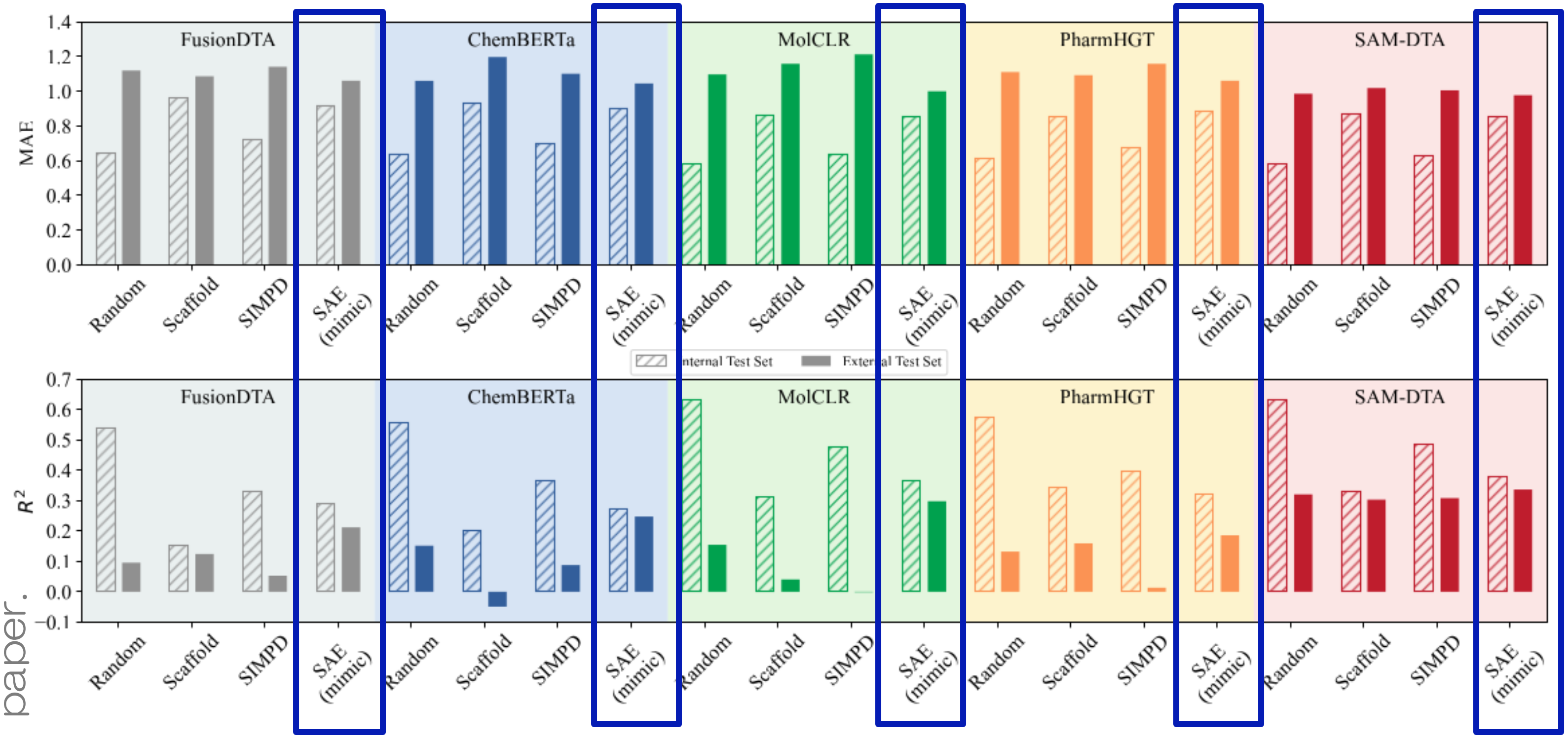


Fig. 5 in the paper.

Perspectives

1. Comments on the paper
2. Why is it interesting for BioComp?

My comments on the paper

Strengths:

- Paper is well-written
- Topic is interesting and their experiments on random splits are useful
- Algorithm is flexible and computationally efficient (even for large data sets)

Weaknesses:

- Experimental results on the "mimic" (unbalanced target distribution) are not impressive (Fig. 4 and 6)
- Does not address three-way splitting (training + testing + validation) but it is discussed in the OpenReview page **[9]**

Your comments?

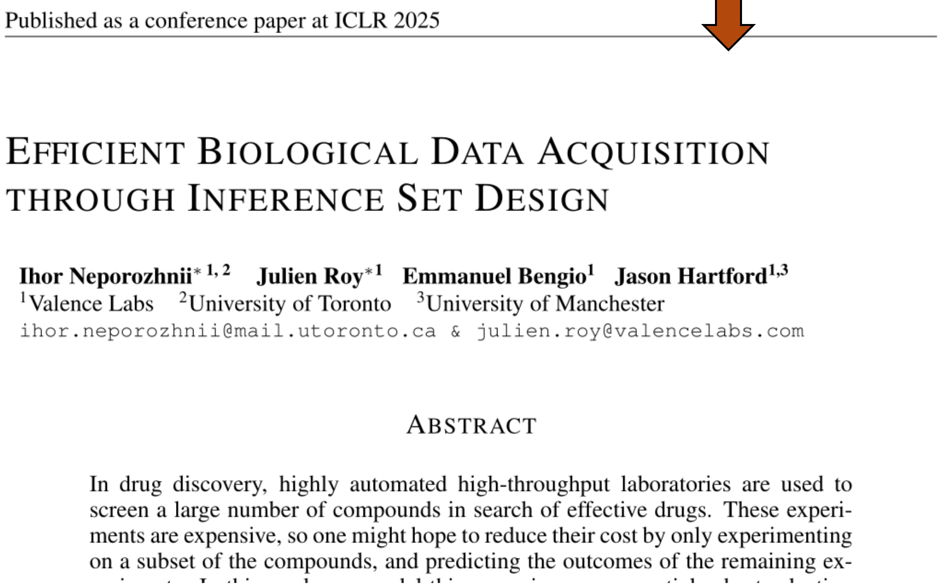
[9] *https://openreview.net/forum?id=j7cyANIAxV*

Why is it interesting for BioComp? Fairer evaluation, model generalizability = better understanding.

Especially for biological data: random splits might be tricky

→ Need to remove / balance out confounders for the target outcome (like in clinical trials!)

Might be connected to active learning in biology: a careful selection of the training set is (iteratively) done (because the training phase is expensive or because data is scarce)



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EFFICIENT BIOLOGICAL DATA ACQUISITION THROUGH INFERENCE SET DESIGN

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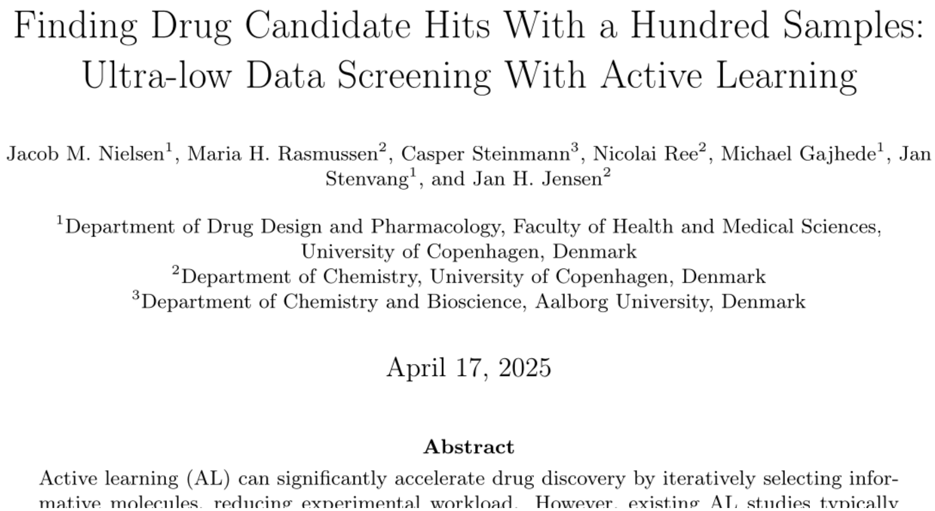
ABSTRACT

In drug discovery, highly automated high-throughput laboratories are used to screen a large number of compounds in search of effective drugs. These experiments are expensive, so one might hope to reduce their cost by only experimenting on a subset of the compounds, and predicting the outcomes of the remaining ex-



Finding Drug Candidate Hits With a Hundred Samples: Ultra-low Data Screening With Active Learning

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April 17, 2025

Abstract

Active learning (AL) can significantly accelerate drug discovery by iteratively selecting informative molecules, reducing experimental workload. However, existing AL studies typically