Can Publishing Neural Networks Expose Confidential Training Data? Risks in Drug Discovery

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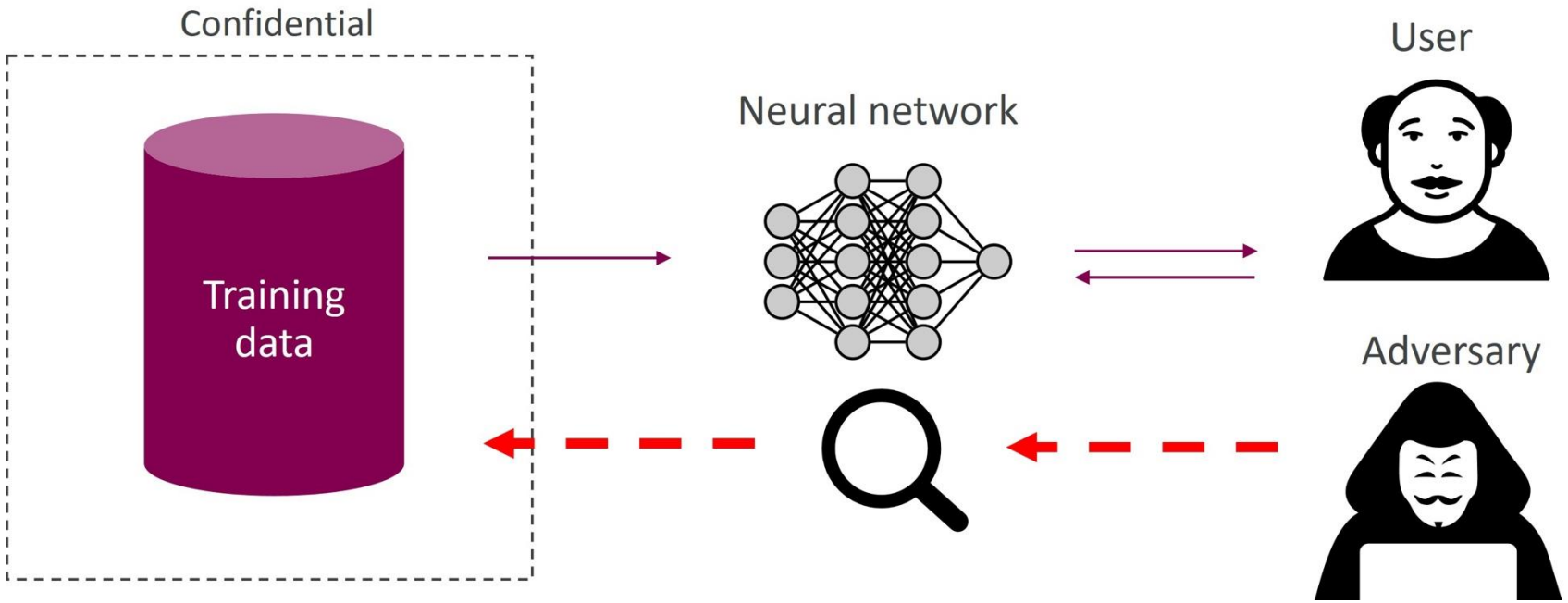
Problem

- In cheminformatics we often work with confidential data
- Open science in machine learning is important for collaboration and innovation[1,2]
- Can we still make our trained models publicly available?

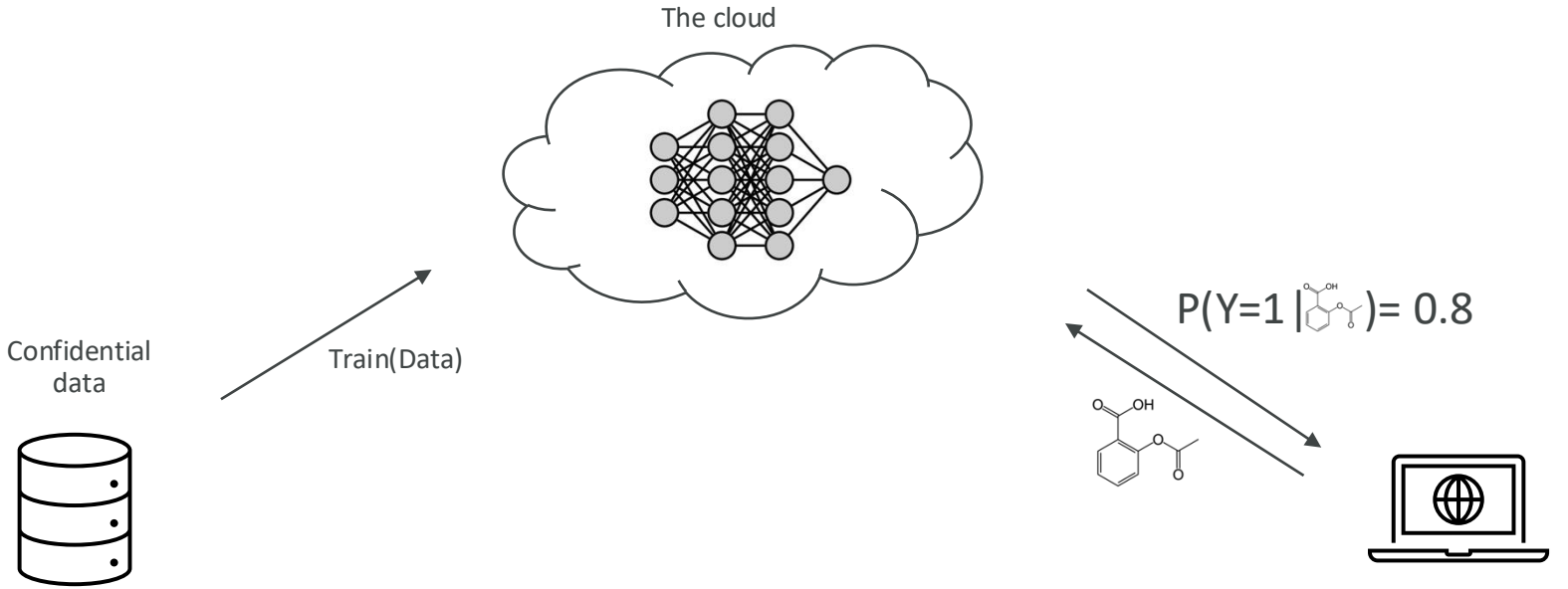


[1]Yash Raj Shrestha, Georg von Krogh, and Stefan Feuerriegel. Building open-source ai. Nature Computational Science, 3(11):908–911, 2023.

[2]Mark Zuckerberg. Open-source ai is the path forward, July 2024. URL https://about.fb.com/news/2024/07/open-source-ai-is-the-path-forward/. Accessed: 2024-09-25.

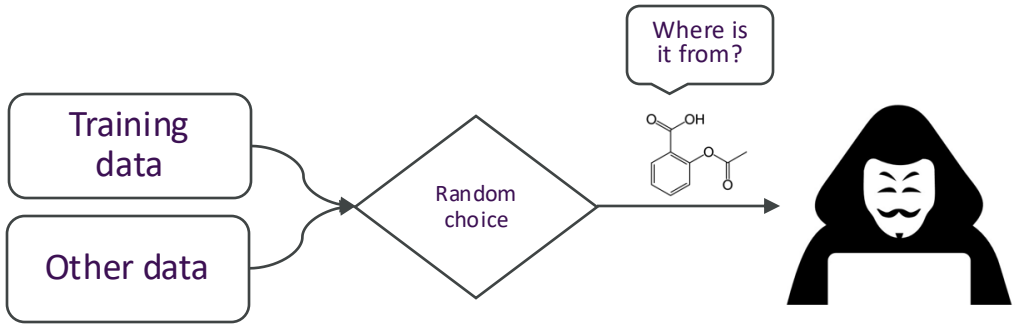
Research question

- How much information about the training data can be identified when you make a model public?
- Here we look at neural networks trained on different tasks for drug discovery
- Black-box setting (no access to weights)



Approach

- To see how much of the training data could be identified, we used membership inference attacks (MIA), which are a widely used method for privacy assessment[1,2,3]



Input: Adversary A, Training Algorithm T, Data distribution Π
Sample n points from Π: $D \sim \Pi^n$
Train model using T on D: $f_\theta \leftarrow T(D)$
Flip a coin: $b \sim \{0, 1\}$
if $b = 0$ **then**
    Sample $z \sim D$
else
    Sample $z \sim \Pi(\cdot \mid z \notin D)$
end if
Let A guess b: $\tilde{b} \leftarrow A(T, \Pi, z, f_\theta(z))$

[1]Reza Shokri, Marco Stronati, Congzheng Song, and Vitaly Shmatikov. Membership inference attacks against machine learning models. In 2017 IEEE symposium on security and privacy (SP), pages 3–18. IEEE, 2017.

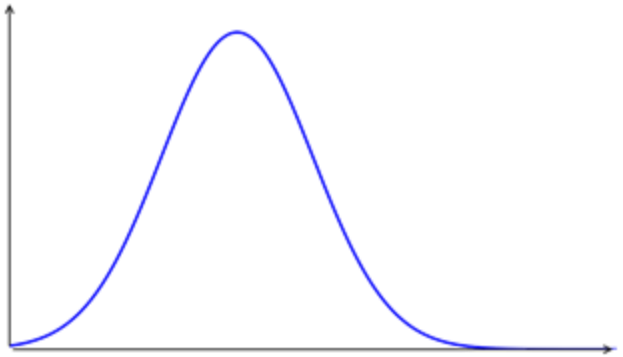
[2]Sasi Kumar Murakonda and Reza Shokri. Ml privacy meter: Aiding regulatory compliance by quantifying the privacy risks of machine learning. arXiv preprint arXiv:2007.09339, 2020.

[3]Nicholas Carlini, Steve Chien, Milad Nasr, Shuang Song, Andreas Terzis, and Florian Tramer. Membership inference attacks from first principles. In 2022 IEEE Symposium on Security and Privacy (SP), pages 1897–1914. IEEE, 2022

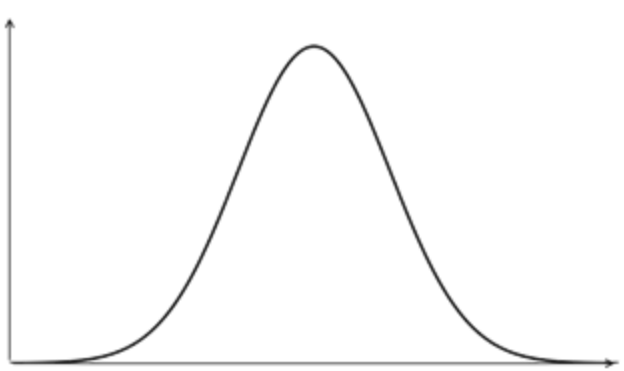
Approach

- We used two different state-of-the-art attacks (LiRA[1] and RMIA[2])
- They rely on having data from a similar distribution to train so-called shadow models

Shadow model predictions for 
from shadow models trained on D_i



Distribution of predictions for 
from shadow models trained on $D_i \cup \{$  $\}$



Target model prediction of 

[1]Nicholas Carlini, Steve Chien, Milad Nasr, Shuang Song, Andreas Terzis, and Florian Tramer. Membership inference attacks from first principles. In 2022 IEEE Symposium on Security and Privacy (SP), pages 1897–1914. IEEE, 2022.

[2]Sajjad Zarifzadeh, Philippe Liu, and Reza Shokri. Low-cost high-power membership inference attacks. In Forty-first International Conference on Machine Learning, 2024.

Datasets

- 4 datasets (all binary classification tasks)

Dataset	Size [# molecules]	Class imbalance [% Positives]
Ability to cross blood-brain barrier (BBB)[1]	1,909	76
Mutagenicity prediction (Ames)[2]	7,255	54
DEL enrichment for carbonic anhydrase IX binding (DEL)[3]	108,528	4.9
hERG inhibition (hERG)[4]	306,341	4.5

[1]Ines Filipa Martins, Ana L Teixeira, Luis Pinheiro, and Andre O Falcao. A bayesian approach to in silico blood-brain barrier penetration modeling. Journal of chemical information and modeling, 52(6):1686–1697, 2012.

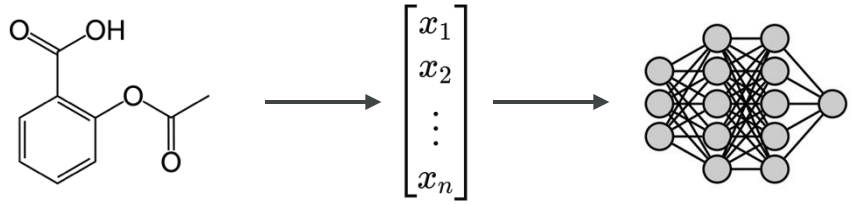
[2]Katja Hansen, Sebastian Mika, Timon Schroeter, Andreas Sutter, Antonius Ter Laak, Thomas Steger-Hartmann, Nikolaus Heinrich, and Klaus-Robert Muller. Benchmark data set for in silico prediction of ames mutagenicity. Journal of chemical information and modeling, 49(9):2077–2081, 2009.

[3]Katherine S Lim, Andrew G Reidenbach, Bruce K Hua, Jeremy W Mason, Christopher J Gerry, Paul A Clemons, and Connor W Coley. Machine learning ondna-encoded library count data using an uncertainty-aware probabilistic loss function. Journal of chemical information and modeling, 62(10):2316–2331, 2022.

[4]Fang Du, Haibo Yu, Beiyan Zou, Joseph Babcock, Shunyou Long, and Min Li. hergcentral: a large database to store, retrieve, and analyze compound-human ether-a-go-go related gene channel interactions to facilitate cardiotoxicity assessment in drug development. Assay and drug development technologies, 9(6):580–588, 2011

Models

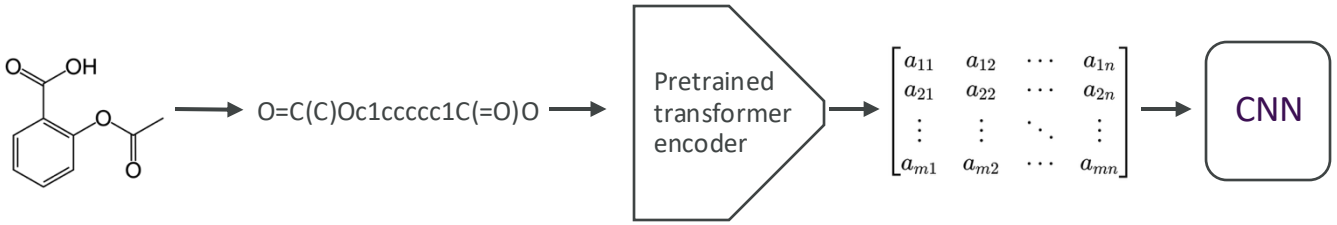
- MLPs on different molecular representations
  - ECFPs
  - MACCS keys
  - RDKitFP



- Message passing neural networks (graph)

[1]

- Transformer with CNN (SMILES)[2]

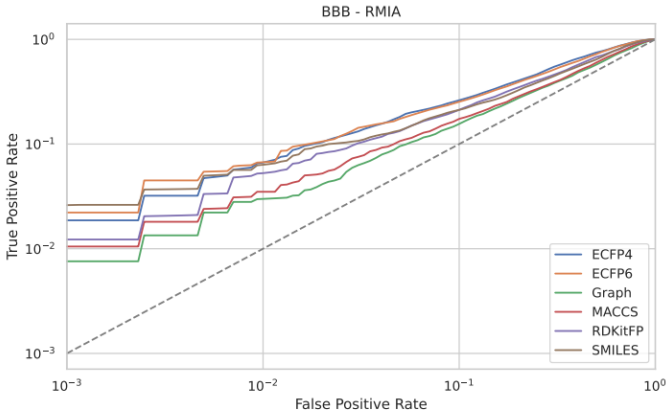


[1]Heid, Esther, et al. "Chemprop: a machine learning package for chemical property prediction." *Journal of Chemical Information and Modeling* 64.1 (2023): 9-17.

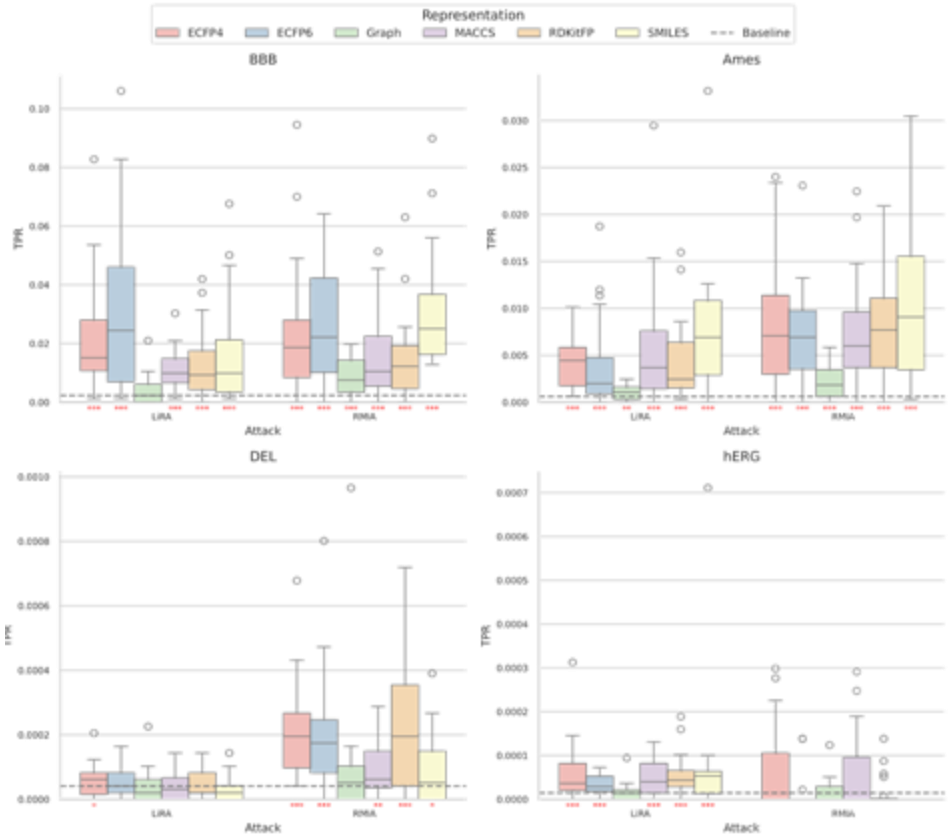
[2]Pavel Karpov, Guillaume Godin, and Igor V Tetko. Transformer-cnn: Swiss knife for qsar modeling and interpretation. Journal of cheminformatics, 12:1–12, 2020.

Results

- Low false positive rates (FPRs) for identifying training data members are most relevant from a privacy perspective[1]
- Identifying training data is consistently possible



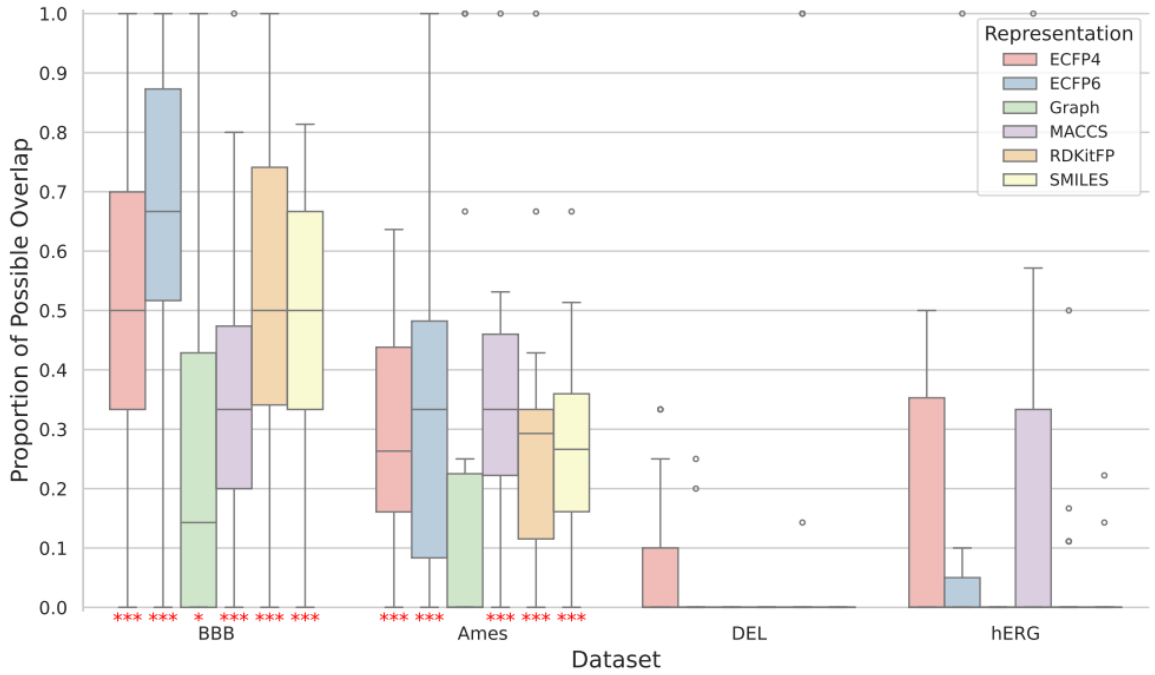
FPR=0:



[1]Nicholas Carlini, Steve Chien, Milad Nasr, Shuang Song, Andreas Terzis, and Florian Tramer. Membership inference attacks from first principles. In 2022 IEEE Symposium on Security and Privacy (SP), pages 1897–1914. IEEE, 2022.

Results

- Could you combine the attacks to get even more information?
- Overlap between the attacks:



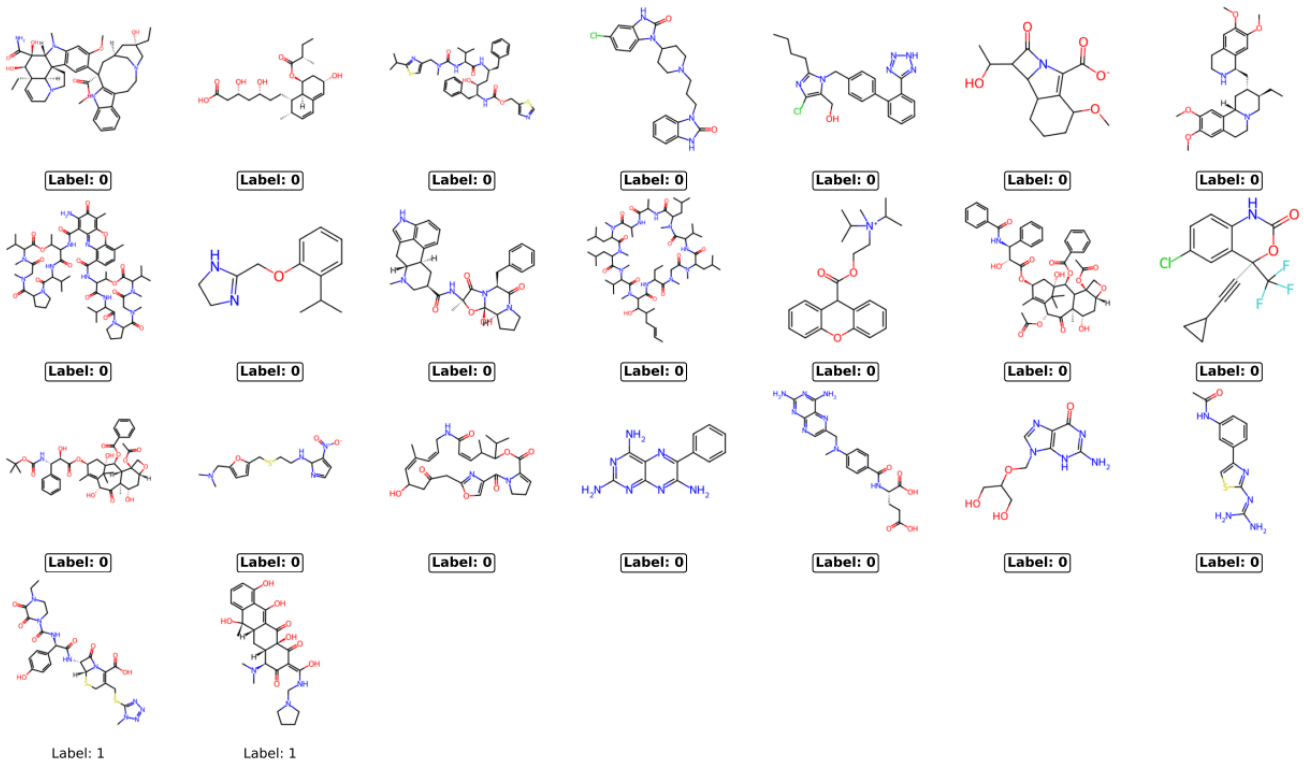
Results

- Minority class is identified more
- Often most important structures

		LiRA		RMIA	
Dataset	Representation	Mean	Significance	Mean	Significance
BBB (0.76)	ECFP4	0.16	***	0.25	***
	ECFP6	0.07	***	0.17	***
	Graph	0.40	**	0.42	**
	MACCS	0.31	***	0.37	**
	RDKitFP	0.19	***	0.31	***
	SMILES	0.21	***	0.20	***
Ames (0.54)	ECFP4	0.54		0.45	*
	ECFP6	0.49		0.45	
	Graph	0.51		0.77	**
	MACCS	0.50		0.53	
	RDKitFP	0.60		0.47	
	SMILES	0.44		0.44	*
Del (0.05)	ECFP4	0.16		0.78	***
	ECFP6	0.12		0.82	***
	Graph	0.00	***	0.43	
	MACCS	0.23		0.69	***
	RDKitFP	0.14	**	0.62	***
	SMILES	0.05	**	1.00	***
hERG (0.04)	ECFP4	0.80	***	0.55	
	ECFP6	0.44		0.47	
	Graph	0.29		0.53	
	MACCS	0.75	***	0.78	***
	RDKitFP	0.66	***	0.76	***
	SMILES	0.72	***	1.00	***

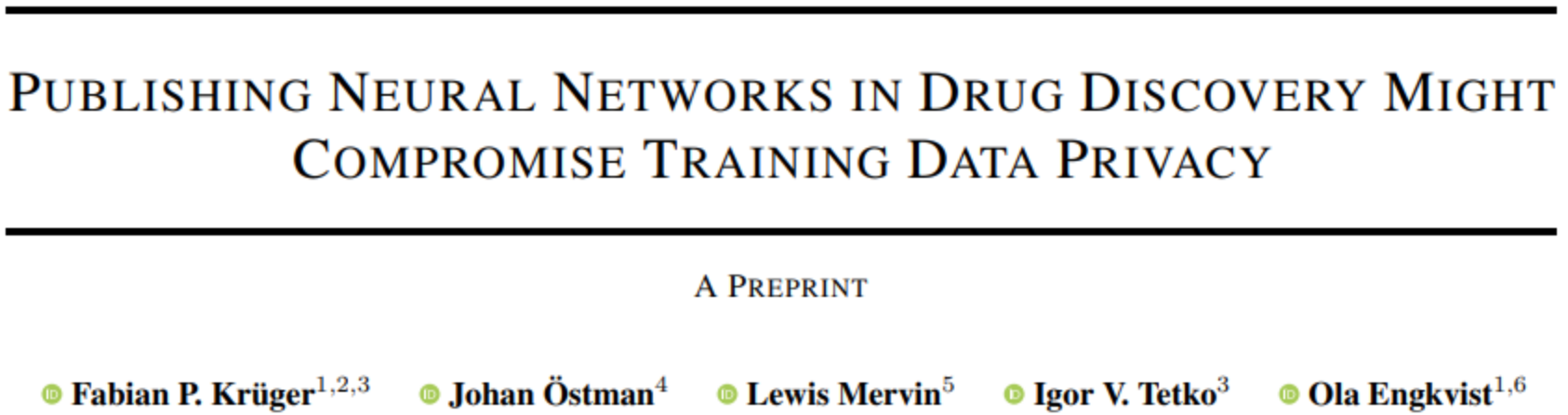
Example case study

- Model trained on ECFP4 for predicting blood-brain barrier crossing
- 23 of 859 training structures identified at FPR=0 with LiRA
- 21 of the 23 structures were from the minority class
- Combining it with RMIA allowed identifying 53 structures at FPR=0



Conclusion

- It is consistently possible to identify parts of the training data, even at FPRs as low as 0 (under some assumptions)
- Combining both attacks allows getting even more information about the training data
- Minority class molecules are easier to identify
- Message passing neural network has the least information leakage
- More information: https://doi.org/10.48550/arXiv.2410.16975


PUBLISHING NEURAL NETWORKS IN DRUG DISCOVERY MIGHT COMPROMISE TRAINING DATA PRIVACY

A PREPRINT

Fabian P. Krüger[1,2,3] Johan Östman[4] Lewis Mervin[5] Igor V. Tetko[3] Ola Engkvist[1,6]

Thank you.

Model classification performance