A Task-Specific Transfer Learning Approach to Enhancing Small Molecule Retention Time Prediction with Limited Data

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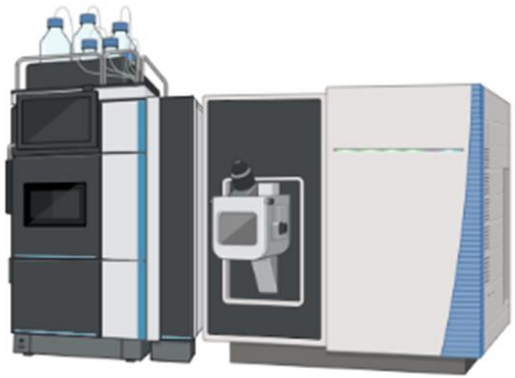
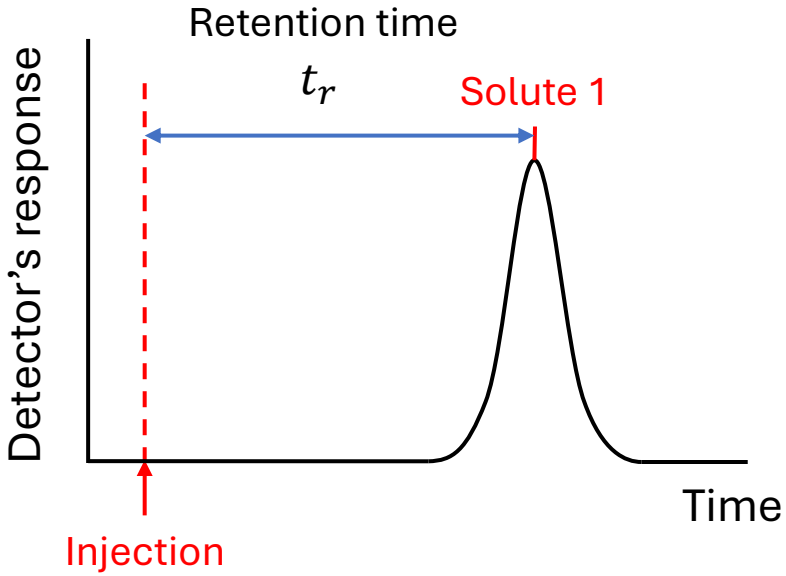
The authors declare no competing financial interest.

Background | LC-MS retention time prediction

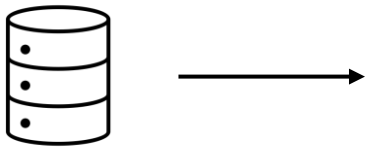


Liquid Chromatography-Mass Spectrometer



Background | LC-MS retention time prediction

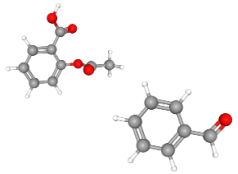
METLIN-SMRT
80,038 small molecules [1]



Small molecules datasets

Neural Networks [1, 2]

under the same standard condition

Molecule	Predicted retention time
	t'_{r1}
	t'_{r2}
.....	.....

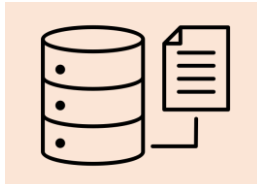
Instrumentation	
LC System	Agilent 1100/1200 series
Mass Spectrometer	Quadrupole-time of flight (Q-TOF) G6538A (Agilent Technologies)
Column	Zorbax Extend-C18 reverse-phase (2.1 × 50 mm, 1.8 µm, Agilent Technologies)

Chromatographic Conditions	
Flow rate	100 µL/min
Mobile phase A	Water + 0.1% formic acid
Mobile phase B	Acetonitrile + 0.1% formic acid
Dead volume	40 µL
Dwell volume	900 µL

[1] Domingo-Almenara X, et al. Nat. Commun. 10, 5811 (2019)
[2] Xue J, et al. Bioinformatics 40.3, btae084 (2024)

Challenge | limited data for different conditions

Retention time dataset (RT) for standard condition
(e.g. METLIN-SMRT [1])



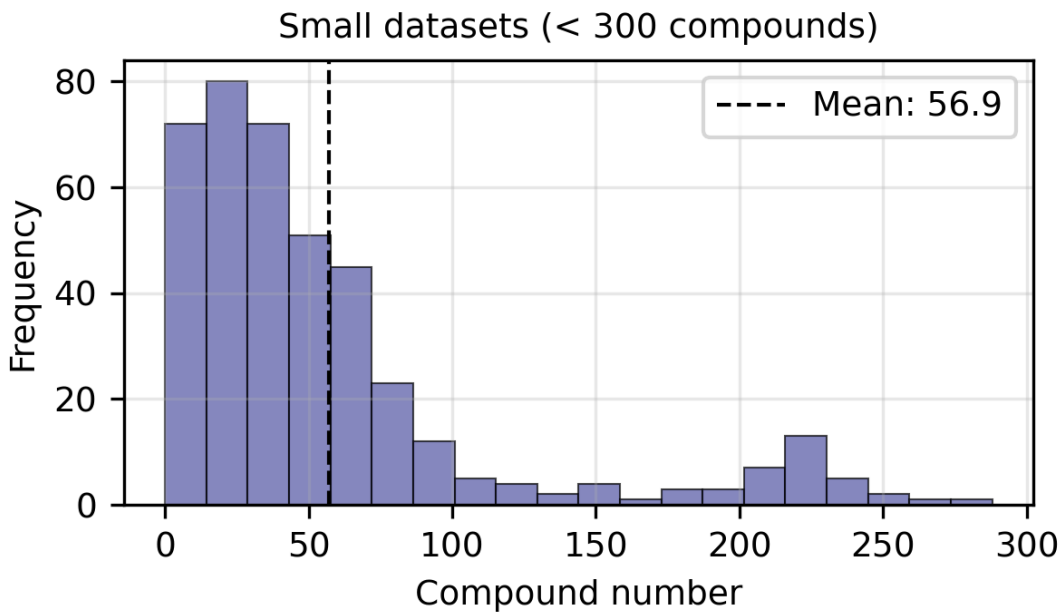
Retention time (RT) dataset for specialized conditions
(e.g. RepoRT [3])

Neural Networks

Insufficient data for training

.....

Only 10 datasets ≥ 300 compounds

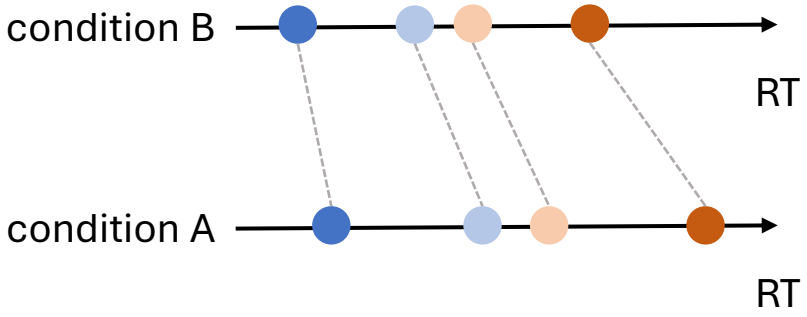


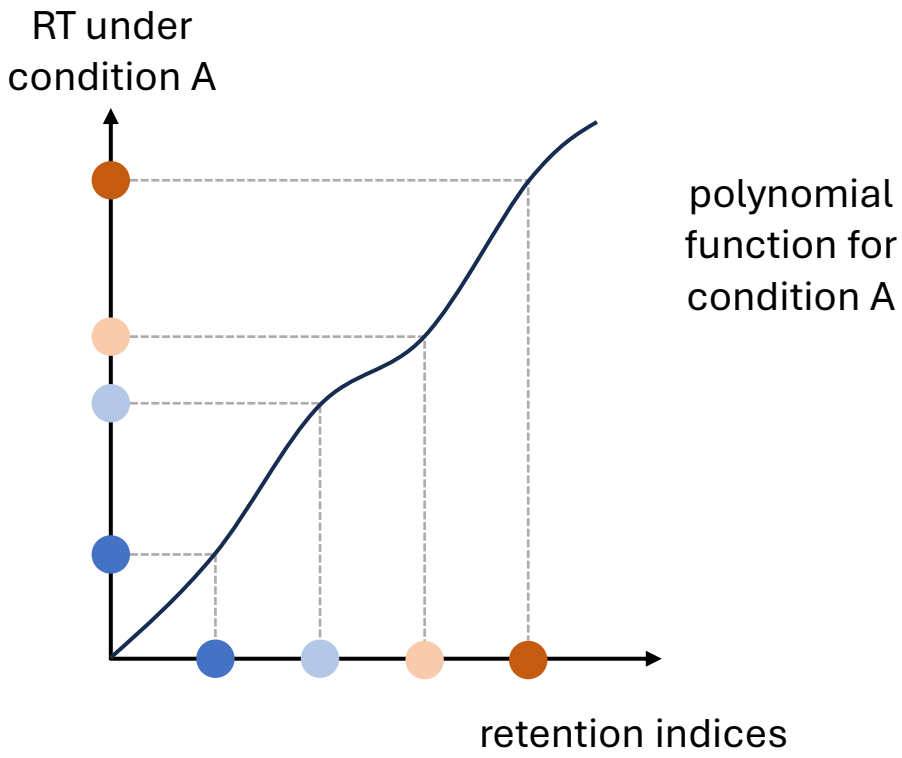
Compounds number (isomeric records) distribution of RT datasets in the RepoRT database [1] before preprocessing

[1] Domingo-Almenara X, et al. Nat. Commun. 10, 5811 (2019)
[3] Kretschmer F, et al. Nat. Methods 21.2, 153-155 (2024)

Challenge | limited data for different conditions

Potential solution 1:
Converting retention times to retention indices [4]

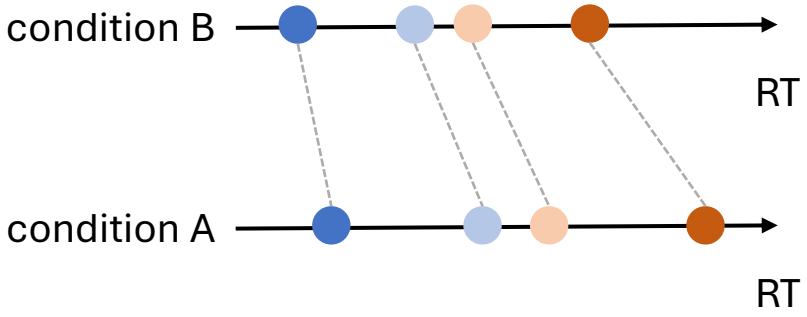


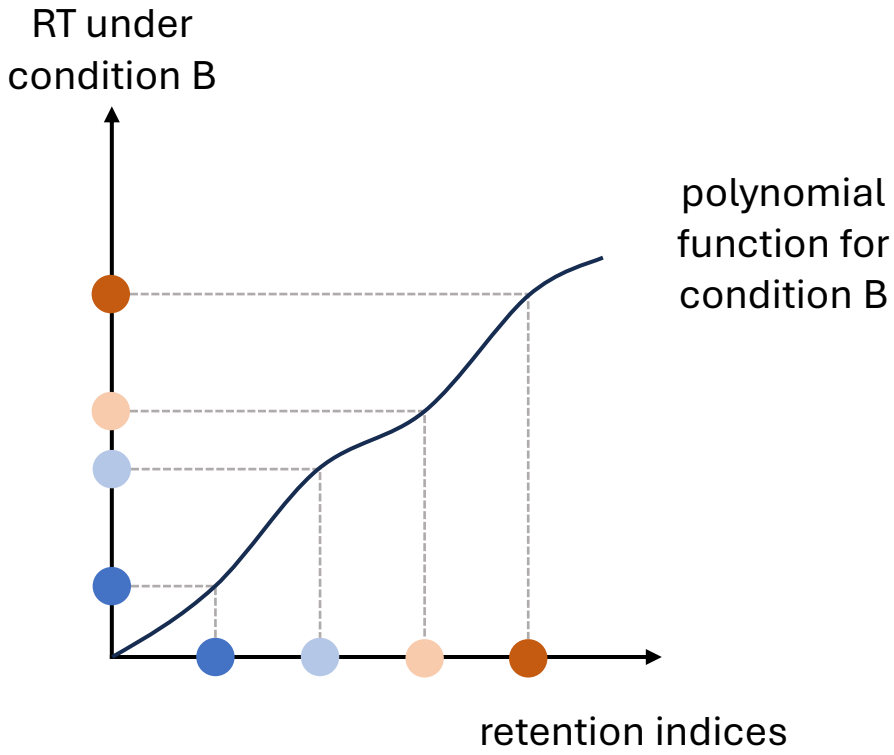


[4] Kretschmer F, et al. arXiv preprint (2024)

Challenge | limited data for different conditions

Potential solution 1:
Converting retention times to retention indices [4]

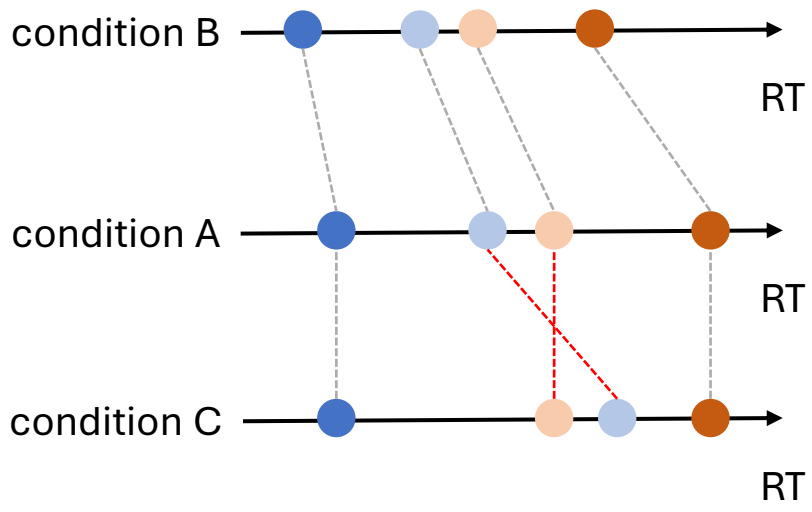


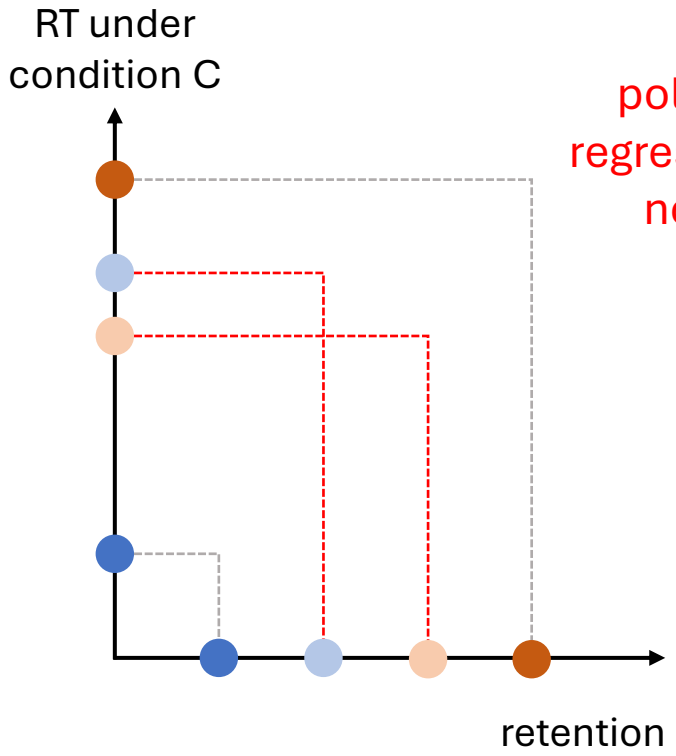


[4] Kretschmer F, et al. arXiv preprint (2024)

Challenge | limited data for different conditions

Potential solution 1: ✗
Converting retention times to retention indices





polynomial regression does not work

Challenge | limited data for different conditions

Potential solution 2: Transfer learning [5, 6]

Upstream dataset,
e.g. METLIN-SMRT [5],
LC-MSMS datasets [6], etc.

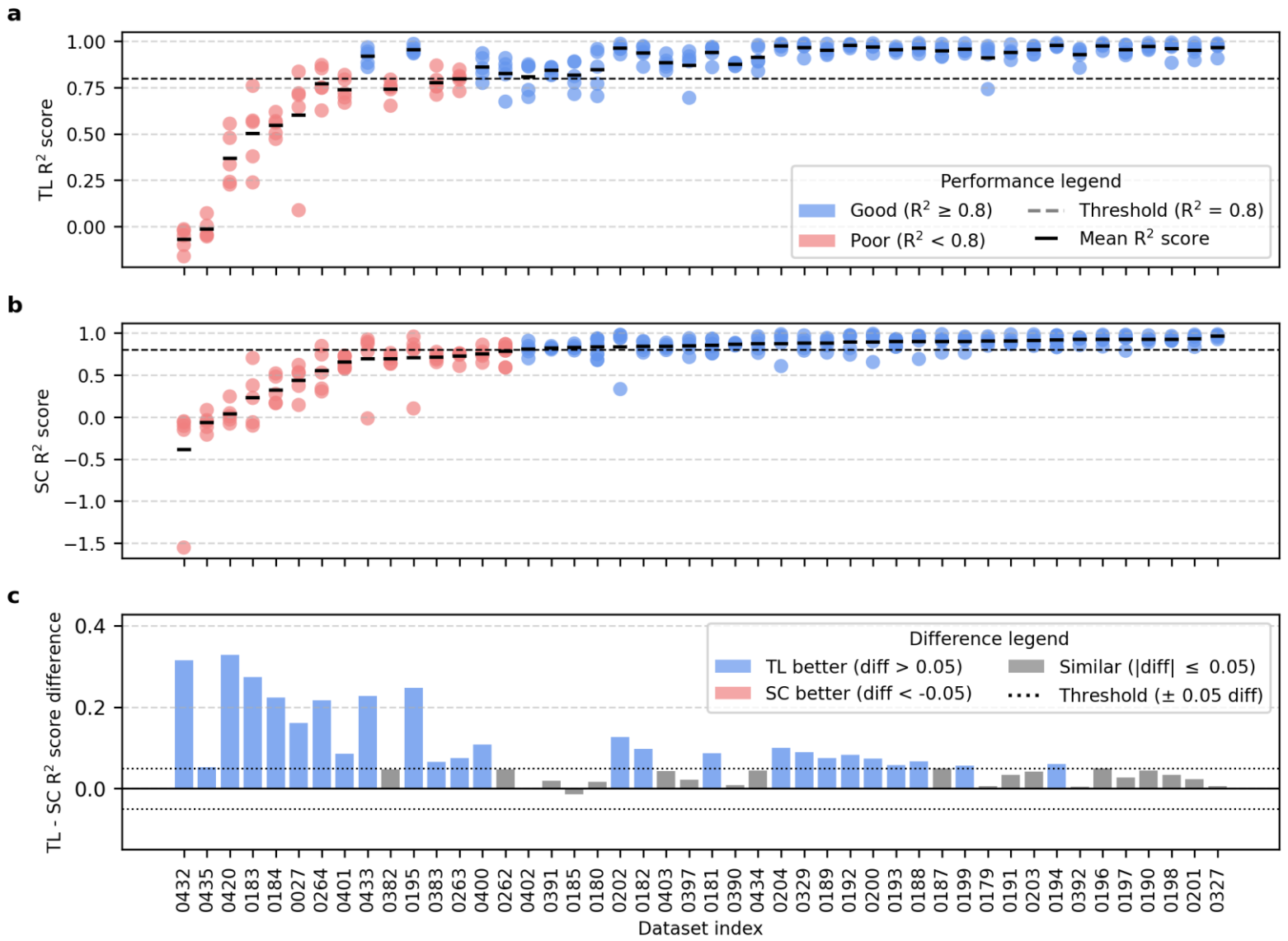
Downstream
dataset

[5] Kwon Y, et al. Anal. Chem. 95.47, 17273-17283 (2023)
[6] Hong Y, et al. Bioinformatics 39.6, btad354 (2023)

Challenge | limited data for different conditions

Potential solution 2: Transfer learning [5]

Performance of Graph Isomorphism Network (GIN) on 45 datasets from the RepoRT database using METLIN-SMRT pre-training [3]



[5] Kwon Y, et al. Anal. Chem. 95.47, 17273-17283 (2023)

Challenge | limited data for different conditions

Potential solution 2: Transfer learning ✗

- Large domain gap between datasets
- Limited downstream data

Upstream dataset, e.g. METLIN-SMRT

Downstream dataset

Our solution:

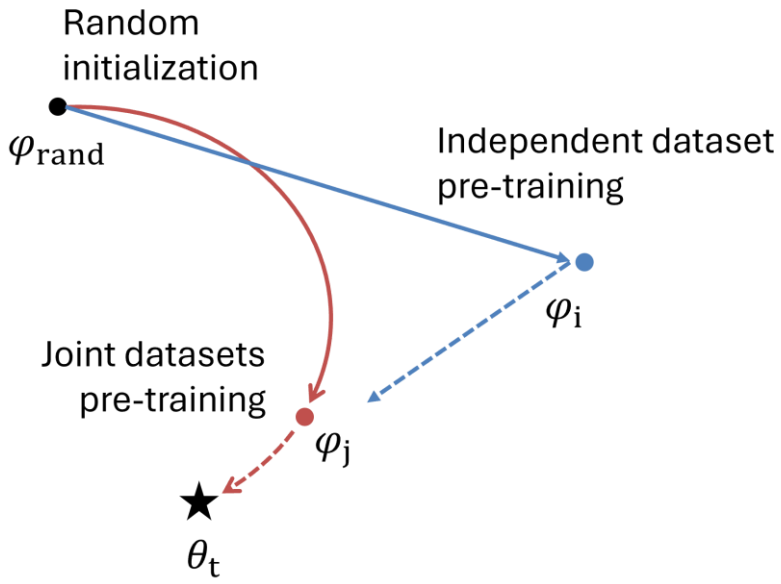
Task-Specific Transfer Learning (TSTL)

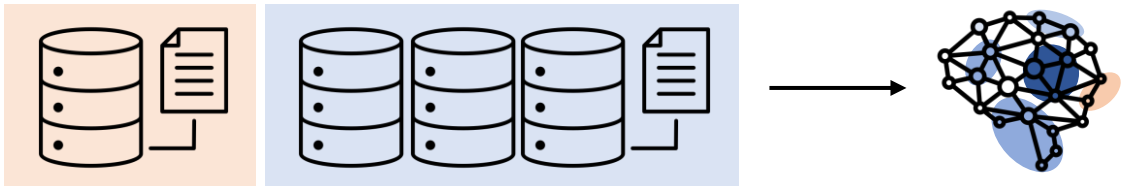
Step 1: Joint datasets pre-training

Step 2: Integration of multiple fine-tuned models

Methodology | task-specific transfer learning

Step 1: Joint datasets pre-training





Upstream dataset
+ Downstream dataset

Efficient fine-tuning

Downstream
dataset

Methodology | task-specific transfer learning

Optimizer methods

$\mathcal{L}(\emptyset)$

pre-trained model

best initialization for
specific downstream task

Methodology | task-specific transfer learning

Optimizer methods

$$\mathcal{L}(\emptyset) = l_t(\theta_t)$$

pre-trained model

best initialization for specific downstream task

fine-tuned model

Methodology | task-specific transfer learning

Optimizer methods

$$\mathcal{L}(\emptyset) = l_t(\theta_t) = l_t(\emptyset - \alpha \nabla_{\emptyset} l_t(\emptyset))$$

inner loop: update θ_t initialized as $\emptyset$ on downstream task

learning rate: α, β

Methodology | task-specific transfer learning

Optimizer methods

$$\emptyset \leftarrow \emptyset - \beta \nabla_{\emptyset} l_{\text{up}}(\emptyset)$$

outer-loop: update randomly initialized $\emptyset$ according to upstream task

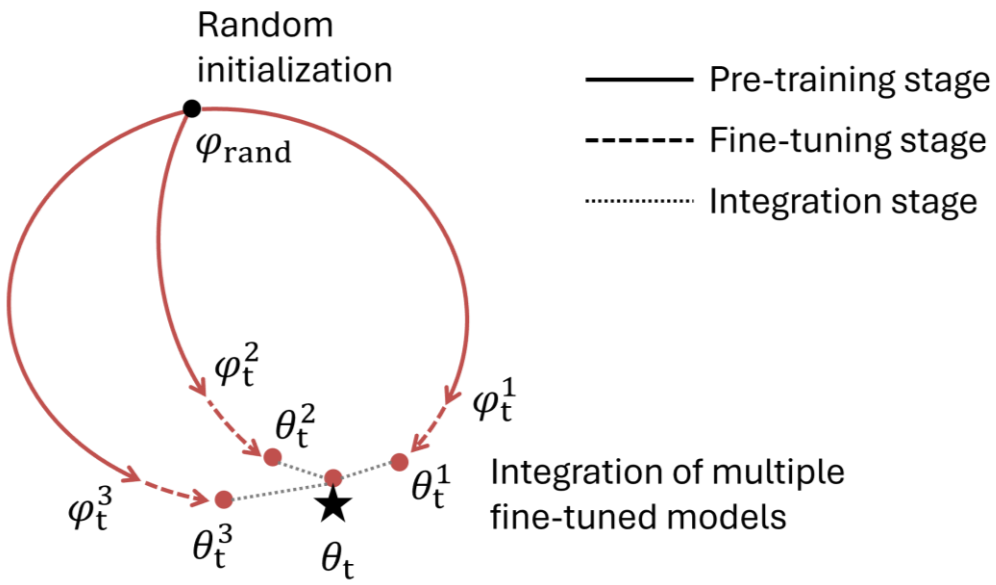
$$\mathcal{L}(\emptyset) = l_t(\theta_t) = l_t(\emptyset - \alpha \nabla_{\emptyset} l_t(\emptyset))$$

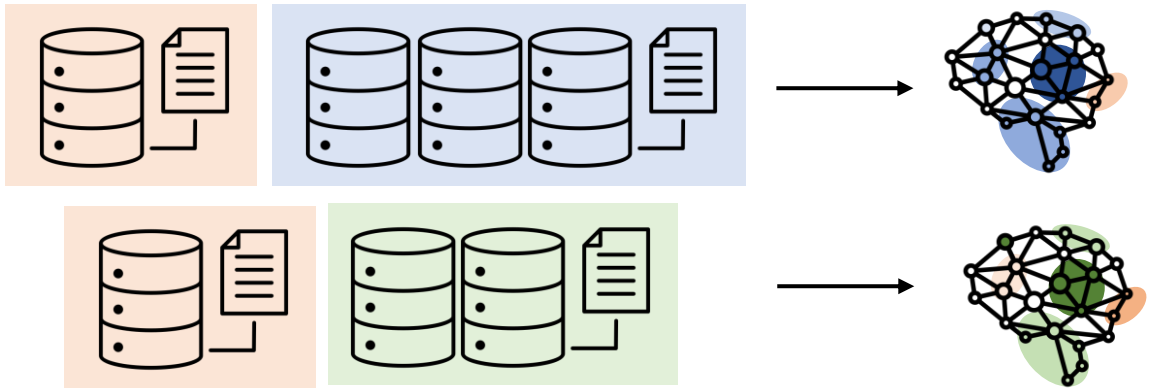
inner loop: update θ_t initialized as $\emptyset$ on downstream task

learning rate: α, β

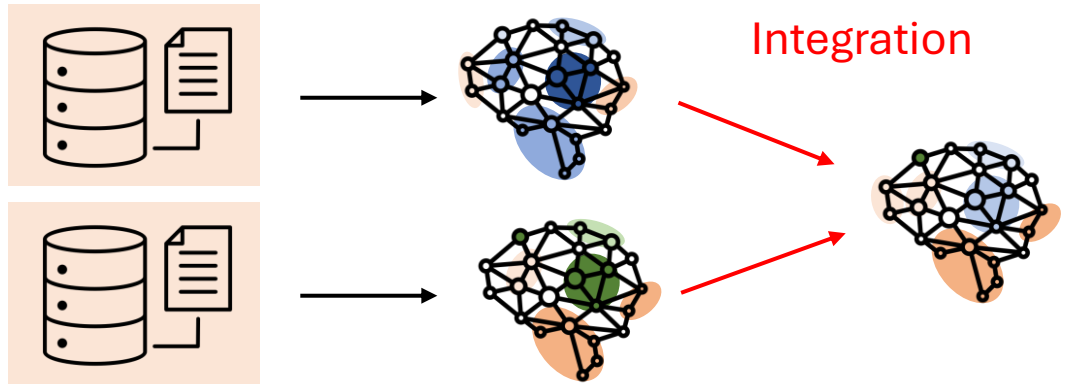
Methodology | task-specific transfer learning

Step 2: Integration of multiple fine-tuned models



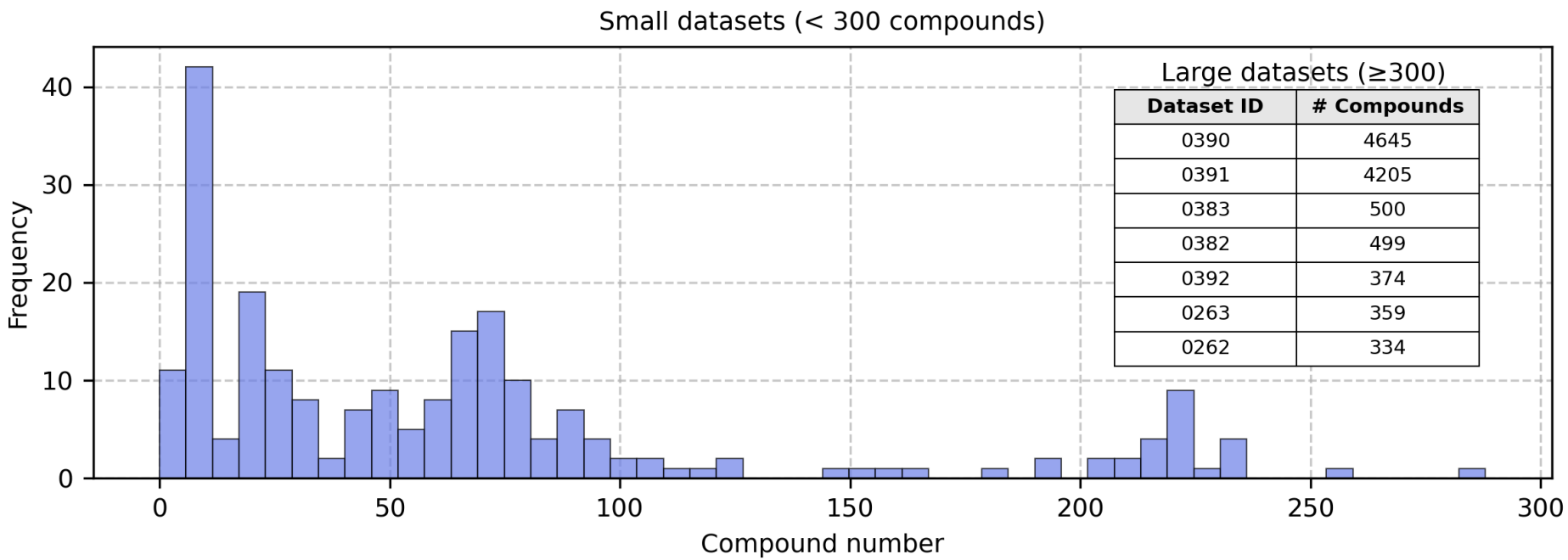


Upstream dataset
+ Downstream dataset



Downstream dataset

Results | data preprocessing



Large datasets (≥300)

Dataset ID	# Compounds
0390	4645
0391	4205
0383	500
0382	499
0392	374
0263	359
0262	334

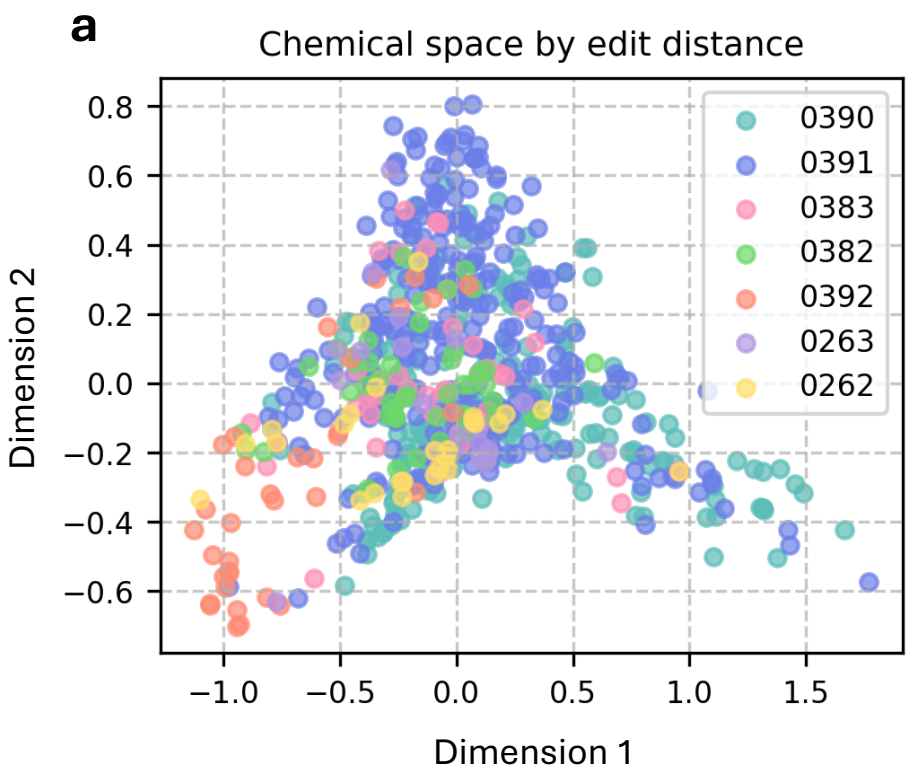
TL-difficult datasets
(TL $R_2 < 0.8$)

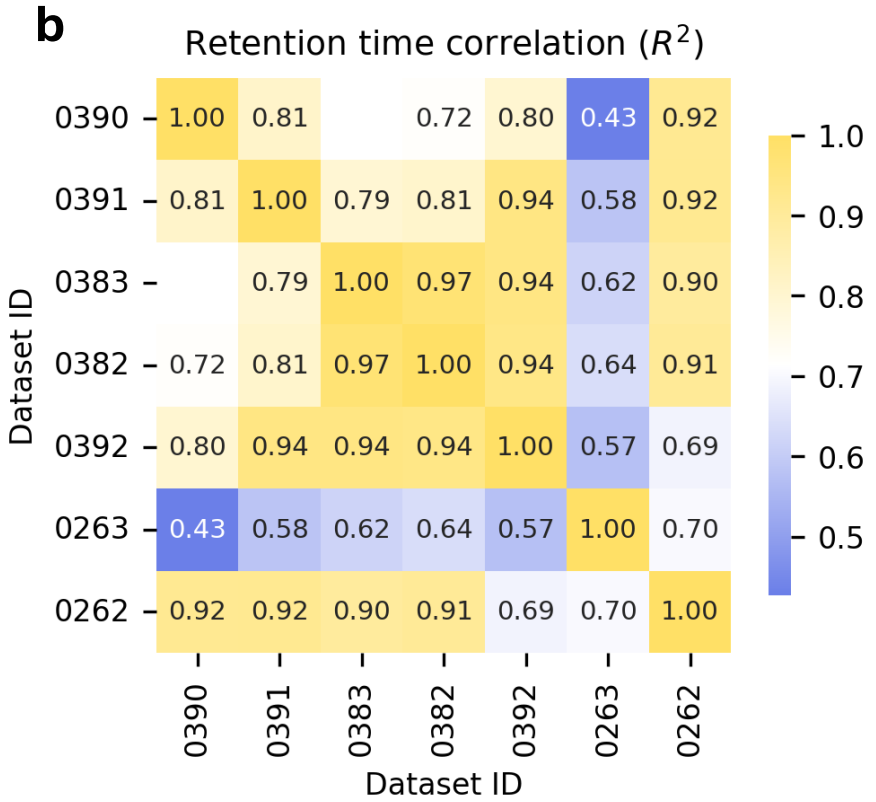
Dataset ID	# Compounds
0027	104
0183	121
0184	124
0264	96
0401	235
0420	162
0432	102
0435	191

Compounds number distribution of RepoRT database [3] after preprocessing

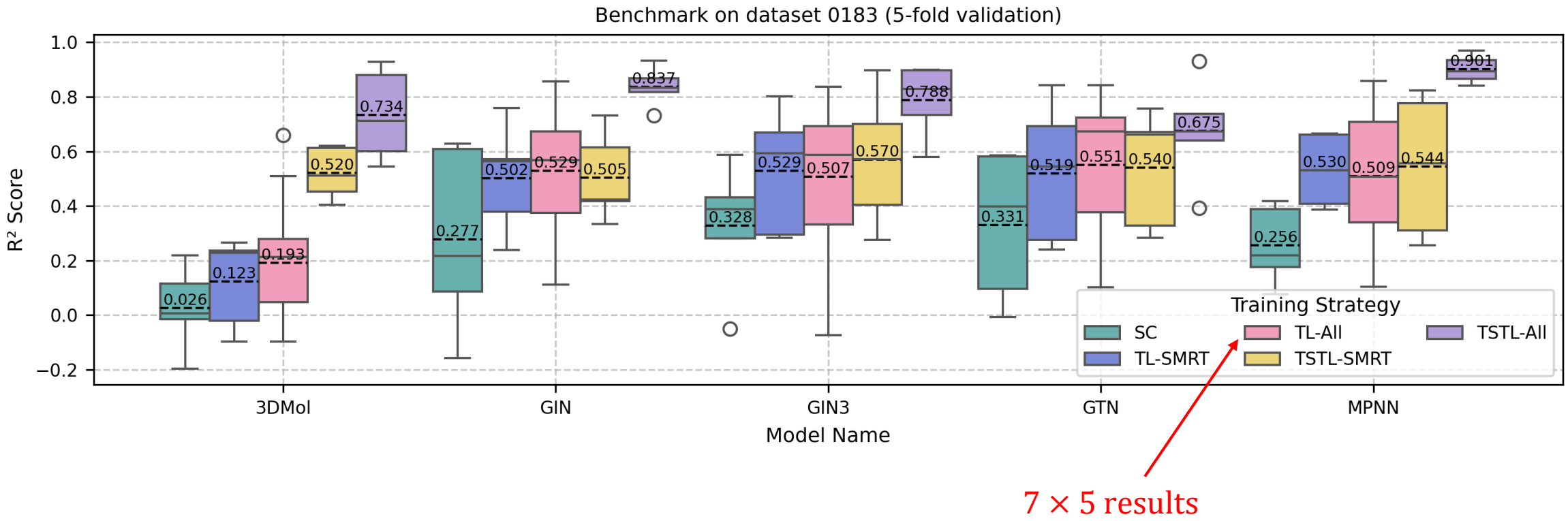
[3] Kretschmer F, et al. Nat. Methods 21.2, 153-155 (2024)

Results | diverse and correlation of up stream tasks

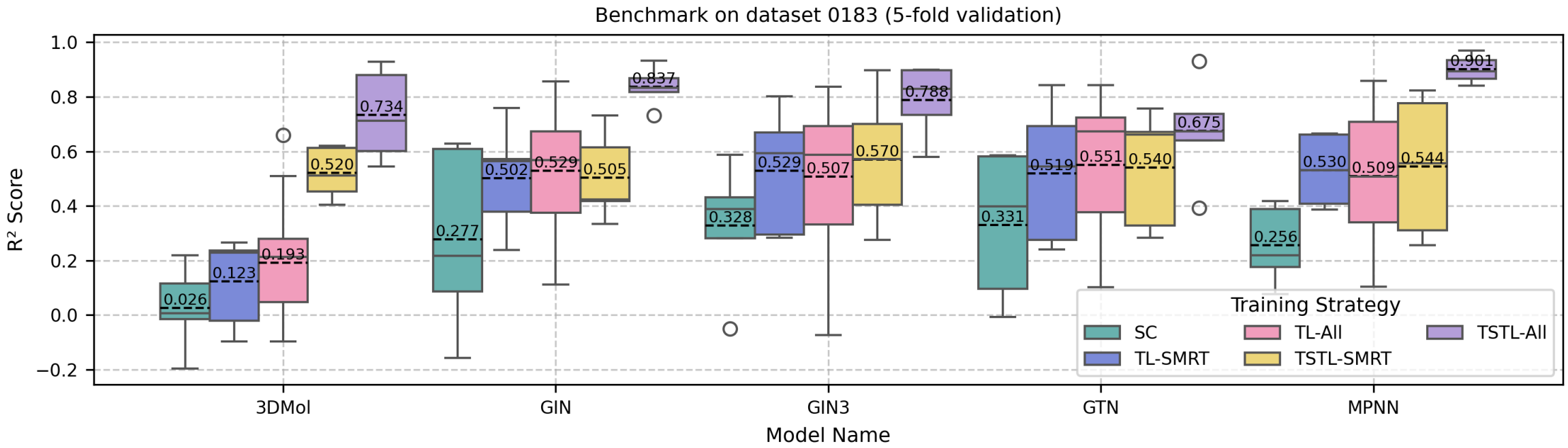




Results | performance of TSTL on retention time prediction



Results | performance of TSTL on retention time prediction



SC ⟹ TL-SMRT ⟶ TL-ALL ⟶ TSTL-SMRT ⟹ TSTL-ALL

Takeaways

- We designed Task-Specific Transfer Learning (TSTL) for training neural networks with limited data
- TSTL incorporates 2 steps: joint pre-training and a greedy integration strategy
- Experiments demonstrate that TSTL outperforms TL on all TL-difficult datasets in RepoRT database

Future work

- Apply TSTL methodology to more predictions
- Enhance integration considering experimental condition correlations

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Thank you!

Manuscript is under preparing.
Follow this GitHub repository for any updates!

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References

[1] Domingo-Almenara, Xavier, et al. "The METLIN small molecule dataset for machine learning-based retention time prediction." Nature communications 10.1 (2019): 5811.

[2] Xue, Jun, et al. "RT-Transformer: retention time prediction for metabolite annotation to assist in metabolite identification." Bioinformatics 40.3 (2024): btae084.

[3] Kretschmer, Fleming, et al. "RepoRT: a comprehensive repository for small molecule retention times." Nature Methods 21.2 (2024): 153-155.

[4] Kretschmer, Fleming, et al. "Times are changing but order matters: Transferable prediction of small molecule liquid chromatography retention times." (2024).

[5] Kwon, Youngchun, et al. "Retention time prediction through learning from a small training data set with a pretrained graph neural network." Analytical Chemistry 95.47 (2023): 17273-17283.

[6] Hong, Yuhui, et al. "3DMolMS: prediction of tandem mass spectra from 3D molecular conformations." Bioinformatics 39.6 (2023): btad354.