Towards human PK prediction: methods, models, and datasets

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13th RDKit UGM

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Introduction

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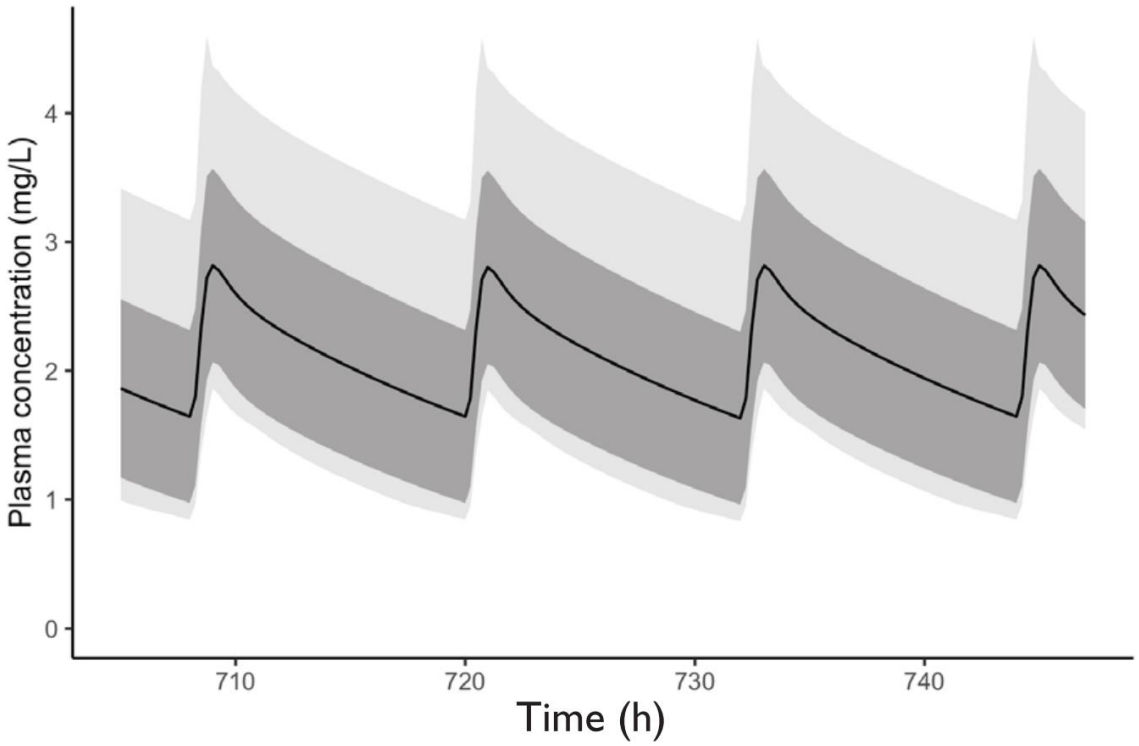
Why do we want to predict human PK?



- PKS Modeling & Simulation predicts the anticipated human dose (AHD) and clinical PK/PD for all compounds and modalities from discovery (~50 projects/yr pre-DC) to Ph1 (~15 projects/yr post DC)
- AHD is an important decision criteria for compound progression, but might come late to drive design decisions
- Providing early AHD can help medchem teams to (de)prioritize compounds and series during lead optimization

Illustrations: DOI: 10.1177/0976500X221111455

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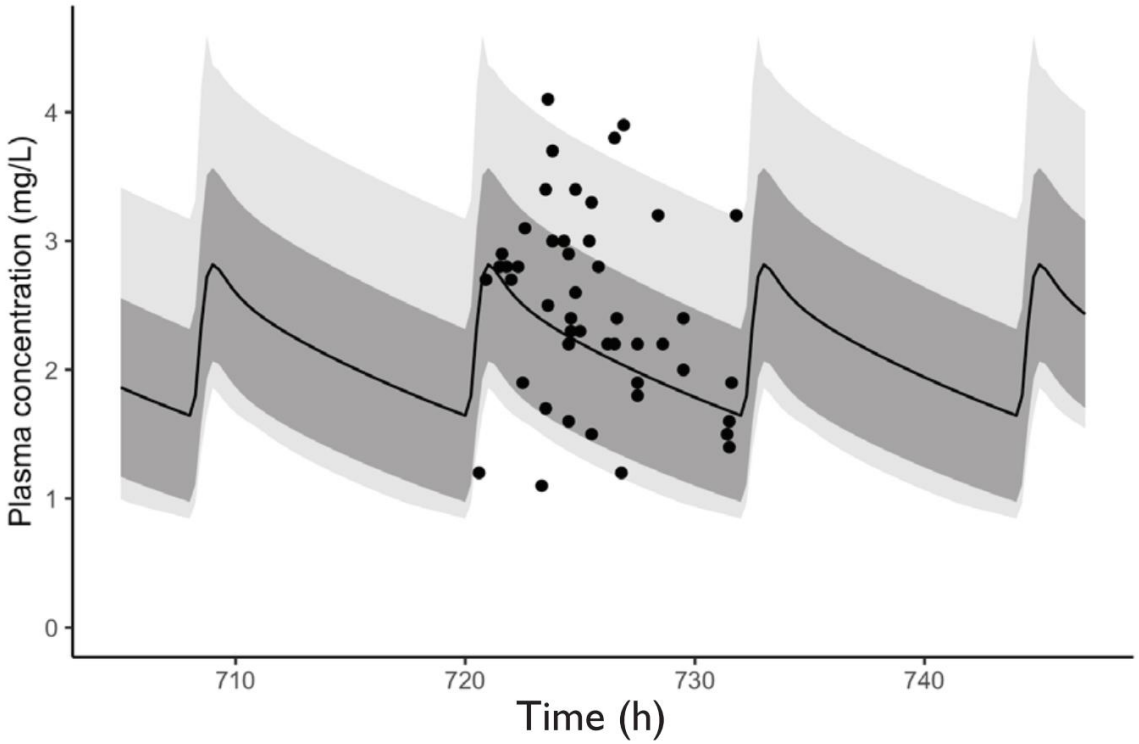
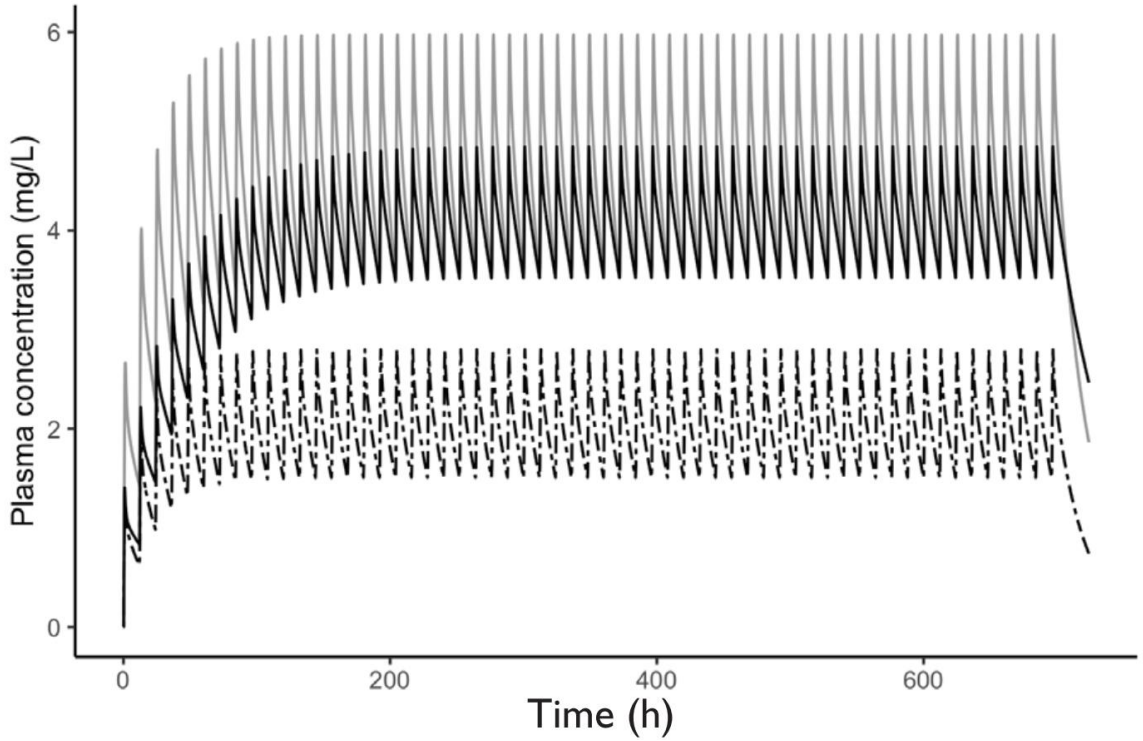


Early AHD allows mapping preclinical data and refine models



Early AHD allows playing various scenarios (dose, dosing regiment)

Illustrations: DOI: 10.1177/0976500X221111455

Two approaches to predict concentration-time profiles

Automated full body PBPK modeling

PBPK (physiologically-based pharmacokinetics) modeling is an established method for human pharmacokinetic modeling

It allows estimation of the drug's PK in various tissues (in particular at the target)

We are working on a fully automated PBPK modeling workflow for early human PK estimation

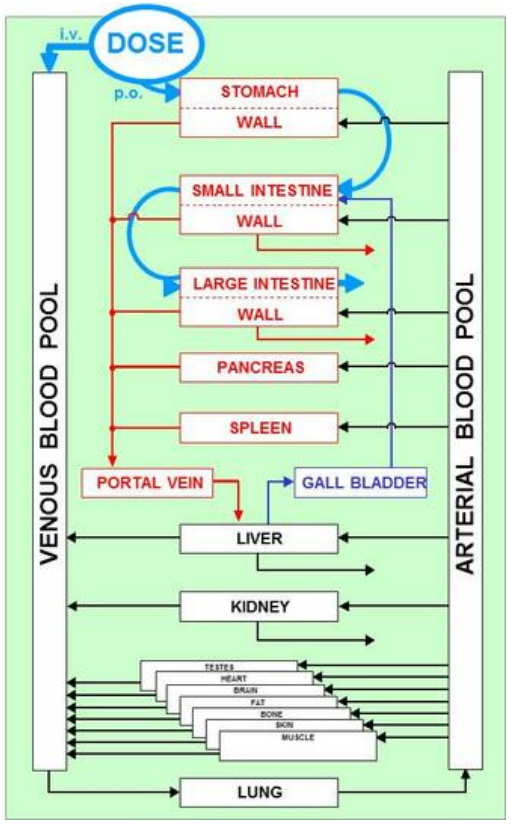


Illustration: docs.open-systems-pharmacology.org

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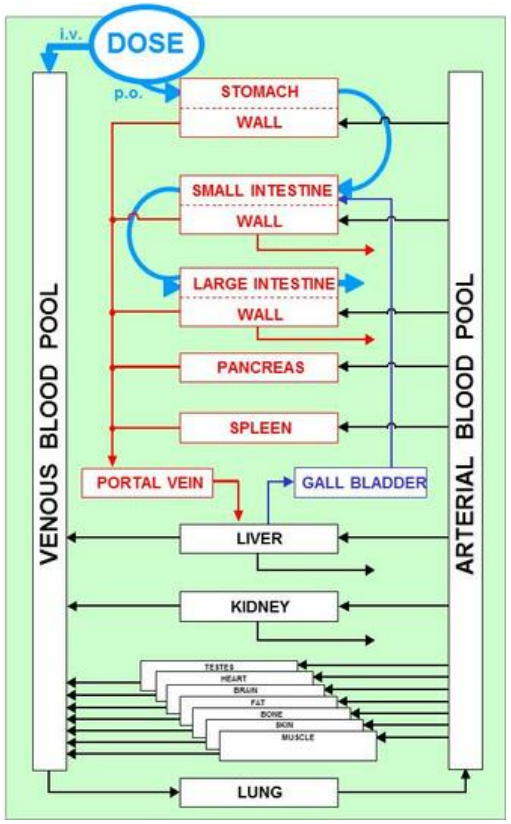

Illustration: docs.open-systems-pharmacology.org

Predicting a mechanistic compartmental PK model

Most machine learning-based prediction efforts have focused on the derived PK parameters instead of C-t profiles

We developed DeepCt, a novel deep learning approach for the prediction of C-t curves from the compound structure, based on the prediction of an underlying mechanistic compartmental PK model

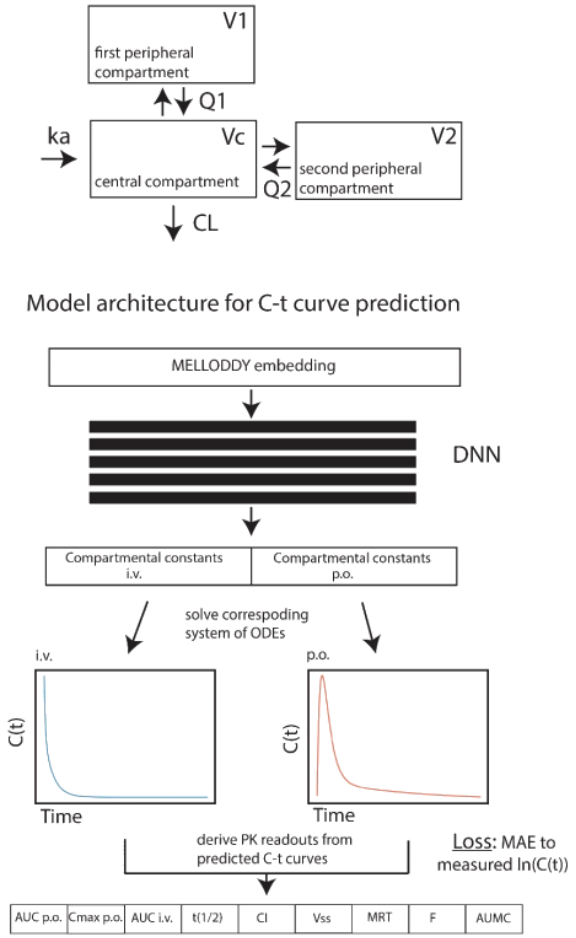

Illustration: DOI: 10.26434/chemrxiv-2024-vg9h7

Automated full body PBPK modeling

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PhysChem and ADME as input parameters

"Due to its physiological basis, most parameters in a PBPK model are independent of substance knowledge or PK measurements. For example, information on blood flow rates, compartment volumes or composition, e.g. in terms of volume fractions of water, proteins, and lipids, can be implemented independently of the substance." *docs.open-systems-pharmacology.org*

Drug-specific parameters will describe its absorption, distribution, metabolism, and excretion; our automated PBPK workflow relies on standard PhysChem and ADME properties:

- halogen atoms count,
- lipophilicity,
- fu_p,
- solubility,
- passive permeability / intestinal permeability,
- ionization,
- blood/plasma ratio, and
- Intrinsic clearance

```python
def get_compound_parameters(row):
    parameters = []
    molecularFormula = row["Molecular Formula"]
    pattern = r'[A-Z][a-z]?\d*|\((?:[^()]*(?:\(.*\))?[^()]*)+\)\d+'
    atoms = re.findall(pattern, molecularFormula)
    for atom in atoms:
        element = re.findall(r'([A-Za-z]+)(\d*)', atom)[0]
        if element[0] in ["Br", "Cl", "F", "I"]:
            parameters.append({
                "Name": element[0],
                "Value": float(element[1]) if element[1] != "" else 1.0
            })
    return parameters
```

$C_{17}H_{17}BrCl_2N_2O$ → [{'Name': 'Br', 'Value': 1.0}, {'Name': 'Cl', 'Value': 2.0}]

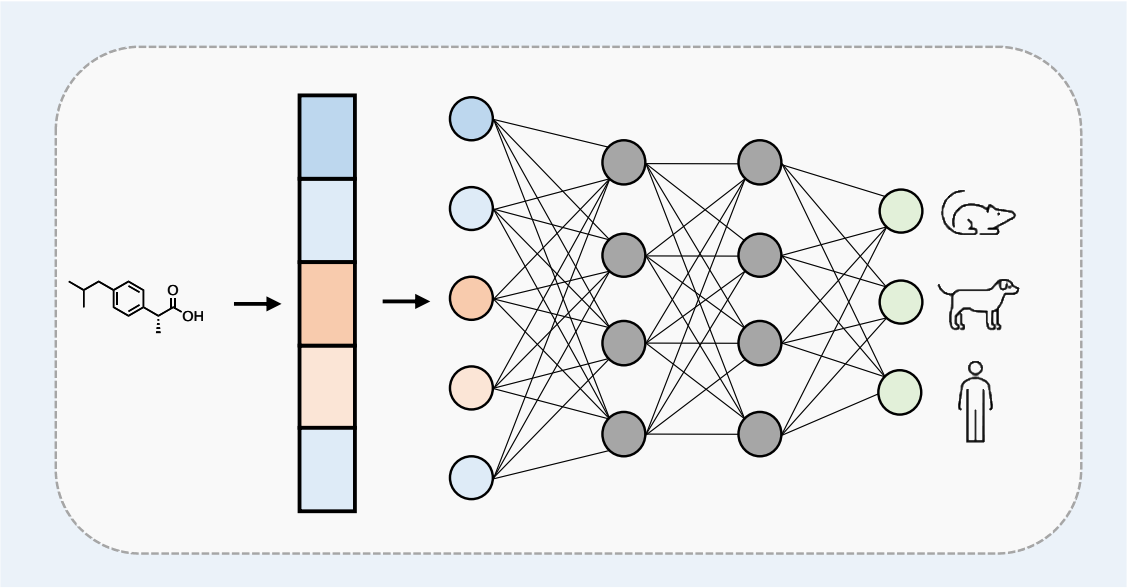
Predicting metabolic clearance

- Hepatic elimination is the major route of drug's clearance and ***in vitro* systems estimate metabolic intrinsic clearance (CLint)** in early phases
- Multi-task (MT) learning strategy where each species was considered as a separate task[1]
- A graph neural network (GNN) was utilized for representation learning[2]
- A **multi-species GNN ensemble model** was generated to predict metabolic clearance[1]

~ # Compounds

Rat	Human	Mouse	Dog	Monkey	Minipig
180,000	112,000	85,000	10,000	8,000	700

Example: Multi-species metabolic clearance model (Multi-task graph neural network, MT-GNN)



[1] R. Rodriguez-Perez, M. Trunzer, N. Schneider, B. Faller, G. Gerebtzoff. Mol Pharm. 2022, 20, 1, 383-394
[2] Yang et al. 2019 JCIM, 59, 3370-3388

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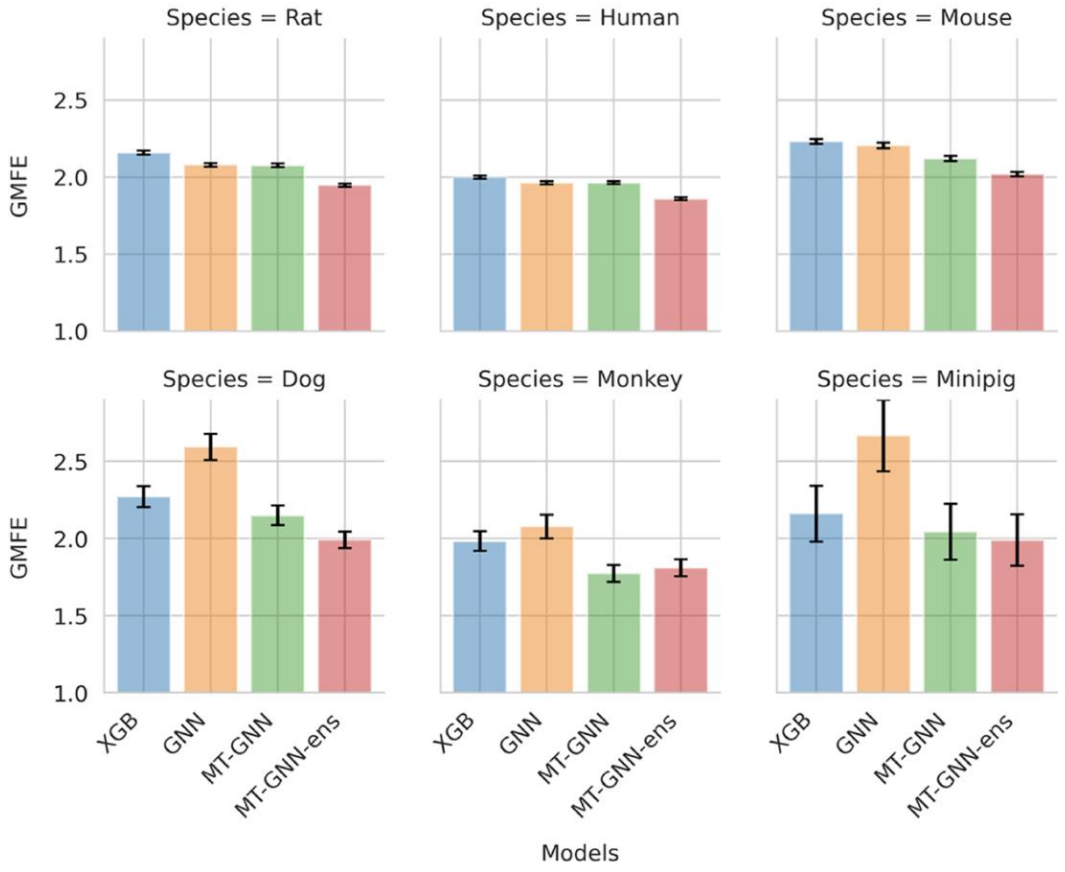

GMFE: Geometric mean fold error

[1] R. Rodriguez-Perez, M. Trunzer, N. Schneider, B. Faller, G. Gerebtzoff. Mol Pharm. 2022, 20, 1, 383-394
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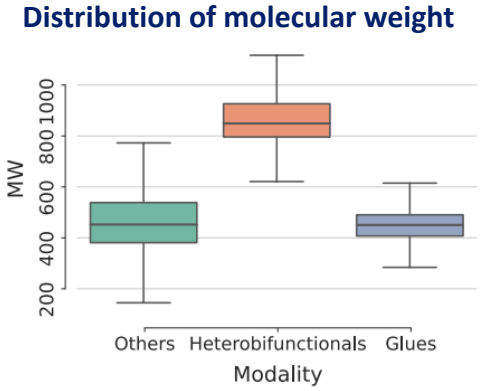
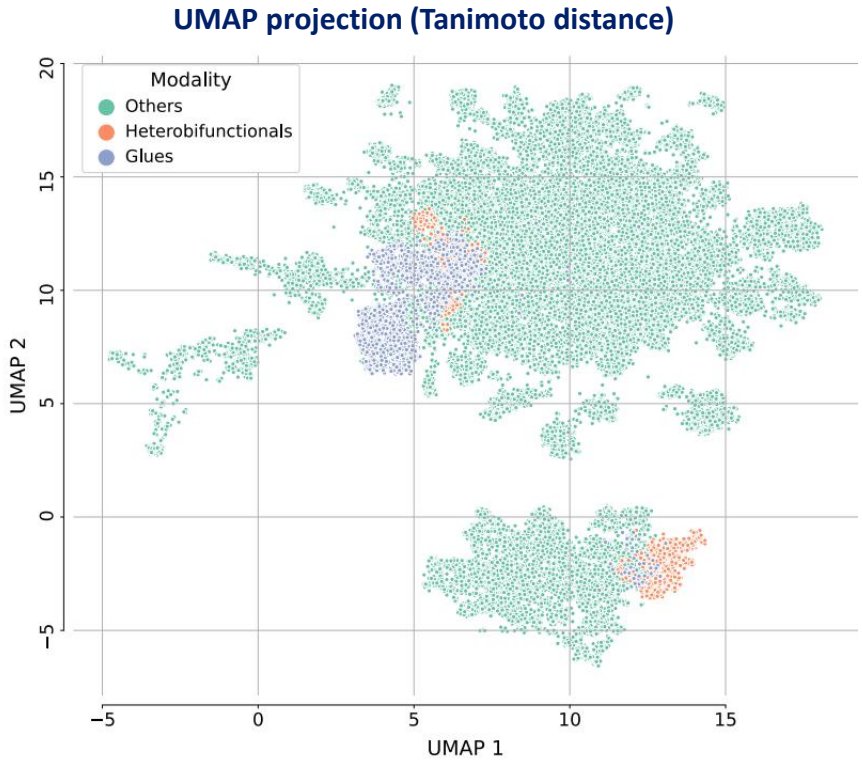
What data shall we use for ML-based QSPR models?
Global vs local models

- In pharmaceutical industry, large amounts of historical data are available for modeling

- Models could be built with data subsets that are more similar to the chemical space of **specific discovery projects or series (local)** or **with all existing data (global)**



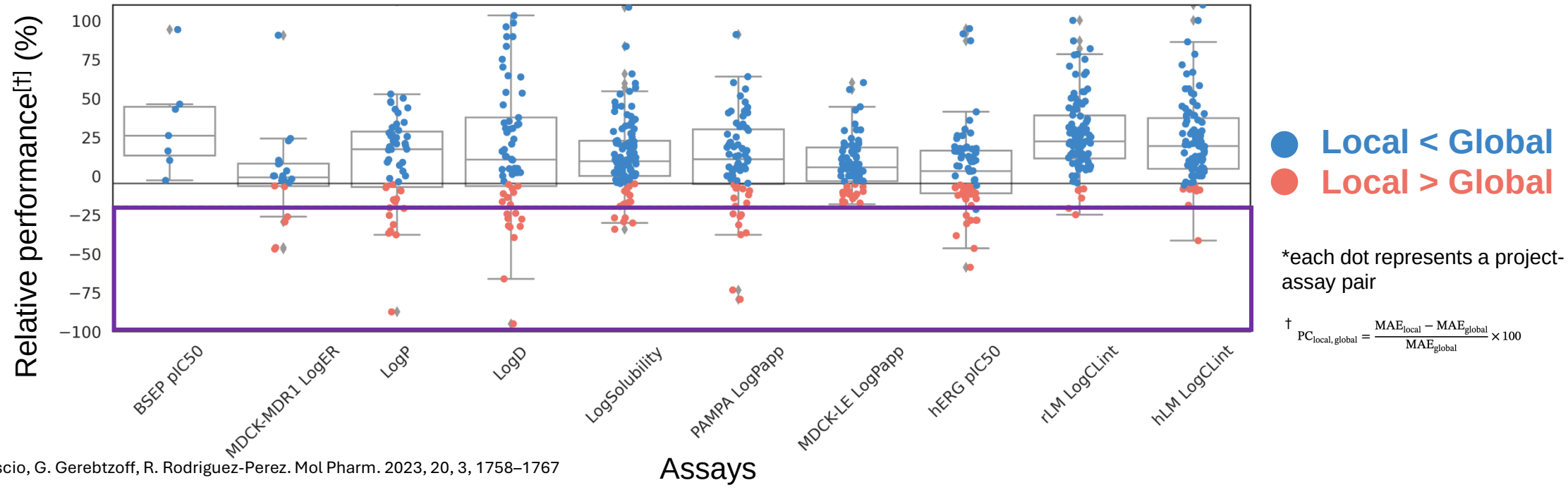


E. Di Lascio, G. Gerebtzoff, R. Rodriguez-Perez. Mol Pharm. 2023, 20, 3, 1758–1767

Per-project performance superior with global ADME models

Comparison across 112 projects, 10 ADME assays, and ~330K compounds

- **Global models perform better than the local models** → Improvements between 3% and 25% in mean absolute error (MAE)
- Only **7%** of the local models present an improvement > 20% over global ADME models



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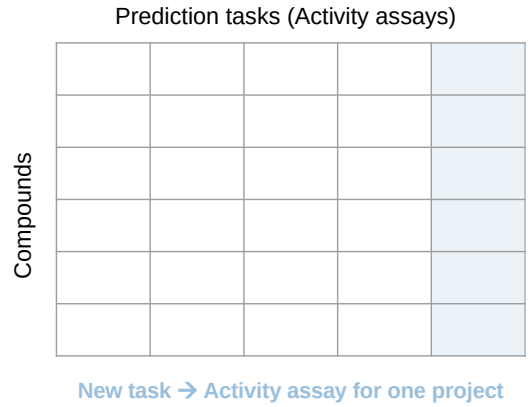
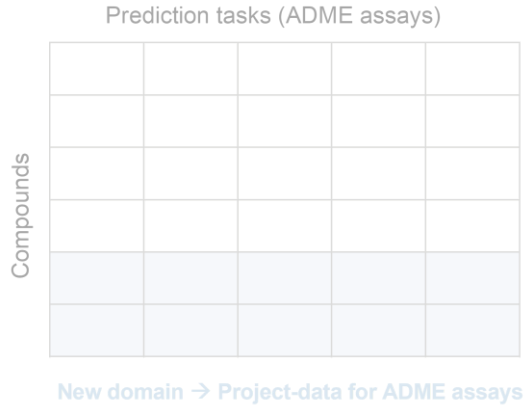
Transfer learning:
New task vs. New domain





For activity predictions, each project has specific activity data (e.g. target) and the data set can be small

Next task: Transfer learning to adapt the model to a new target or assay

M. Stanley et al. NeurIPS Datasets and Benchmarks 2021

For ADME predictions, projects rely on the same assays but have a specific chemical space of interest, where data might be limited

New domain: Transfer learning to adapt the model to the project-specific domain

A. Fluetsch, E. Di Lascio, G. Gerebtzoff, R. Rodriguez-Perez. Mol Pharm. 2024, 21, 4, 1817–1826

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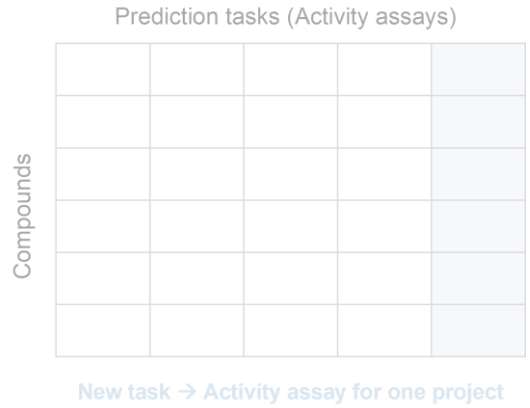

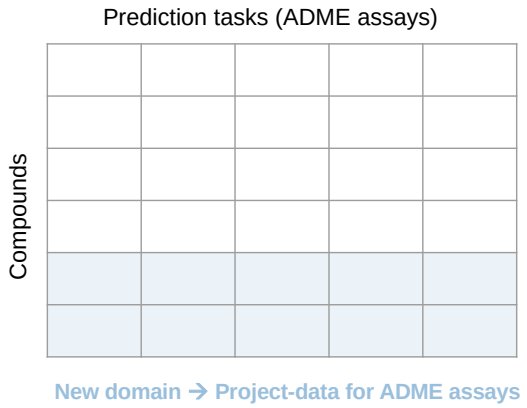

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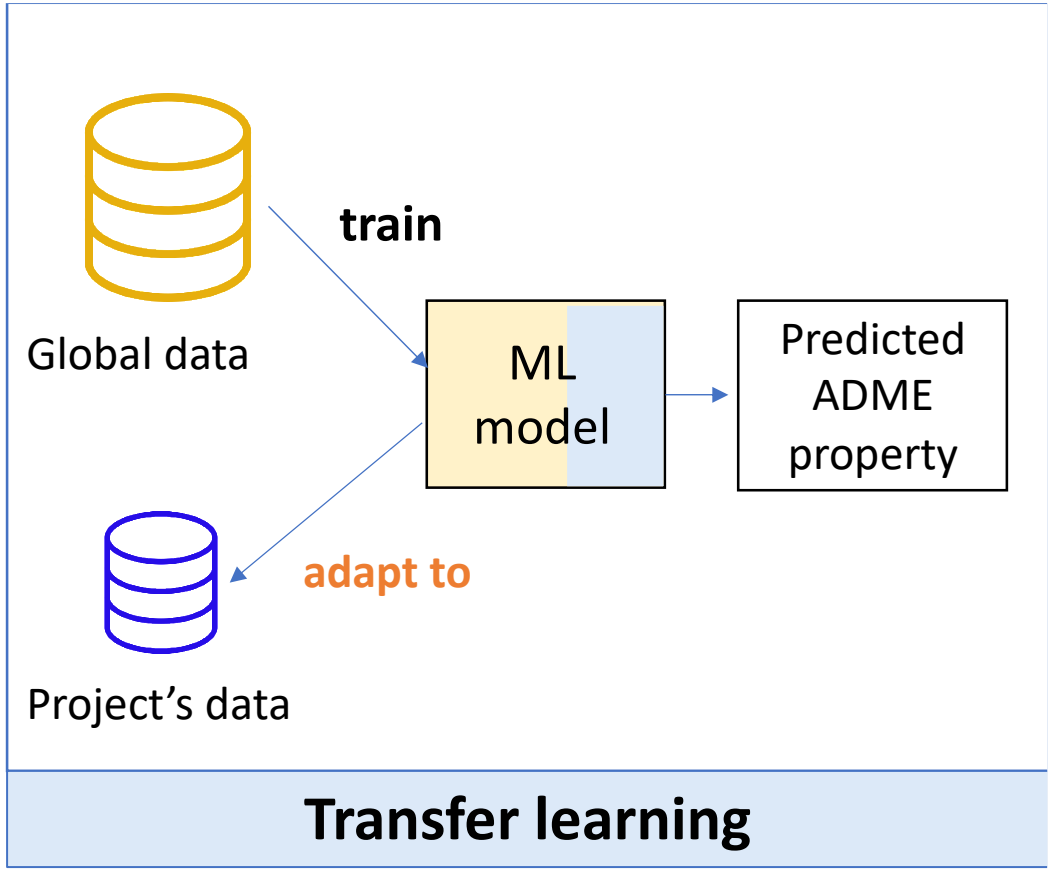
Transfer learning for ADME endpoints

- **Adapting ML models for the prediction of ADME properties to specific drug discovery projects**[1]
- **Different transfer learning approaches were investigated to leverage both**
  - **historical ADME data (global model), and**
  - **project-specific data (local model)** for refining model predictions

- **Case study:** Global ADME models were built with GNNs (message passing + feed-forward neural networks)[1-3]



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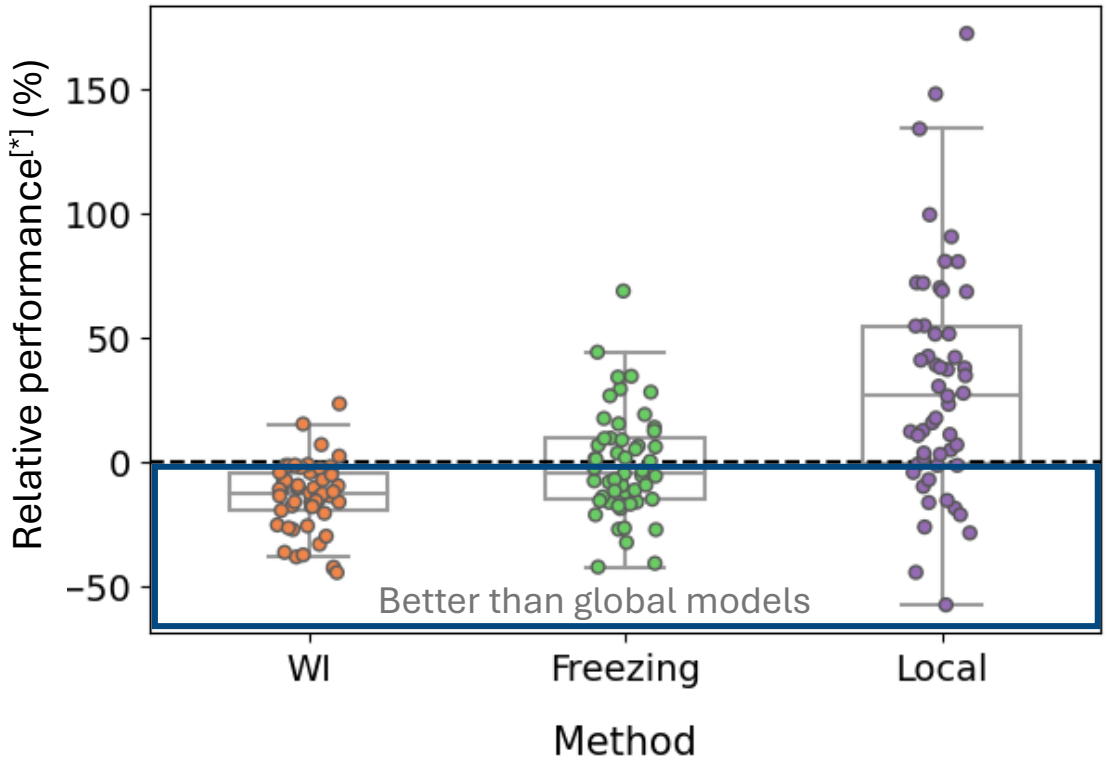
[3] R. Rodriguez-Perez, M. Trunzer, N. Schneider, B. Faller, G. Gerebtzoff. Mol Pharm. 2022, 20, 1, 383-394

Transfer learning:
Project-specific ADME data modeling

- Two transfer learning strategies:
  - **weights' initialization (WI) – fine-tuning the complete GNN**
  - **message-passing neural network freezing**
- Relative performance[*] was compared for of global models vs. transfer learning or **local models**
- **Transfer learning by WI led to lower prediction errors**

$$^{*}\mathrm{PC}_{\mathrm{local,\,global}} = \frac{\mathrm{MAE}_{\mathrm{local}} - \mathrm{MAE}_{\mathrm{global}}}{\mathrm{MAE}_{\mathrm{global}}} \times 100$$

Rat metabolic clearance predictions (CL_{int})



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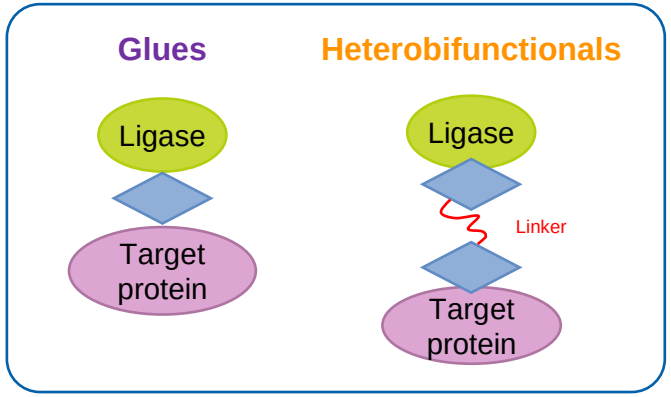
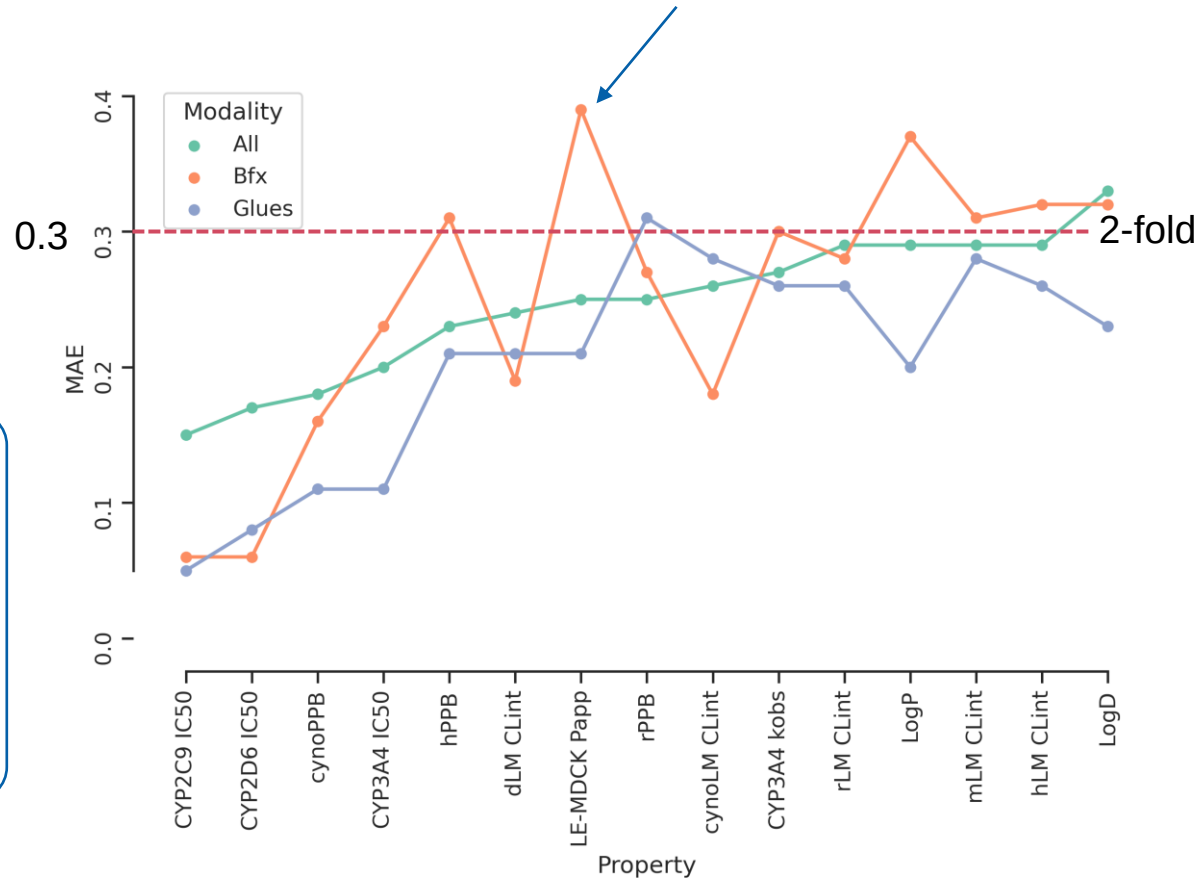
Are ML-based QSPR models applicable to targeted protein degraders (TPDs)?

- MAE of global models are shown for **glues**, **bifunctionals**, and **all modalities**
- Consistent performance for all modalities and TPDs → ML is applicable to TPDs
- In many assays, predictions for glues have the lowest errors



Induction of selective protein degradation through the intracellular ubiquitin-proteasome system

Model refinements were investigated

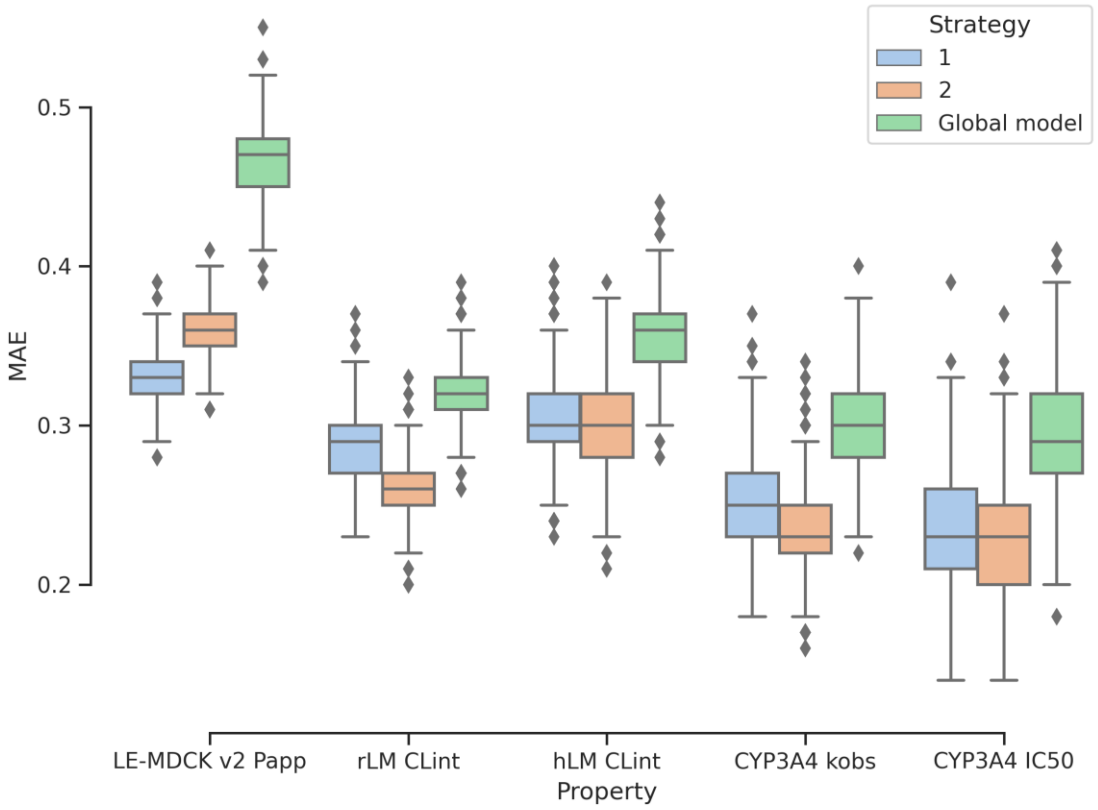


G. Peteani, T. Huynh, G. Gerebtzoff, R. Rodriguez-Perez. Under review

Transfer learning: The new modality of TPDs

- Performance of original and refined models (transfer learning) on **heterobifunctional TPDs**
- Reported are performance metrics for the **original** model & two fine-tuning strategies:
  - using **newest data**
  - using **all heterobifunctional data**

- Models' fine-tuning offered more accurate predictions for heterobifunctionals



G. Peteani, T. Huynh, G. Gerebtzoff, R. Rodriguez-Perez. Under review

DeepCt: predicting concentration-time profiles

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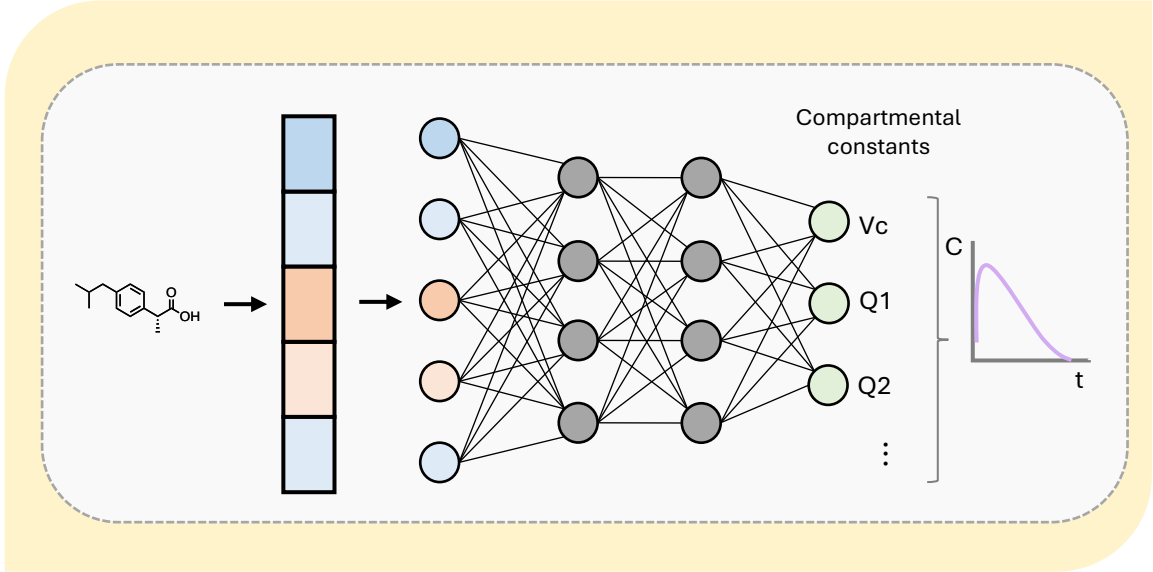
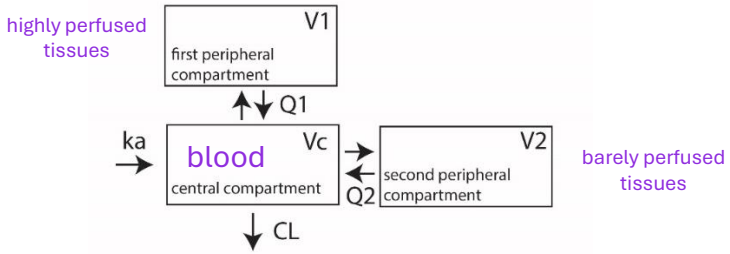
DeepCt: Deep learning model to predict concentration – time profiles from PK studies

- A deep learning model as built to predict concentration-time (C-t) profiles from chemical structure
- The model predicts the constants of a 2-compartmental model, and then the C-t profiles can be generated
- The loss is calculated on the predicted vs. experimental C-t curves



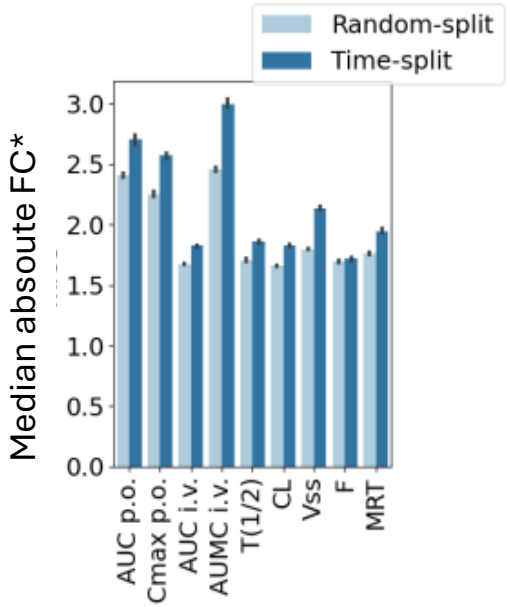


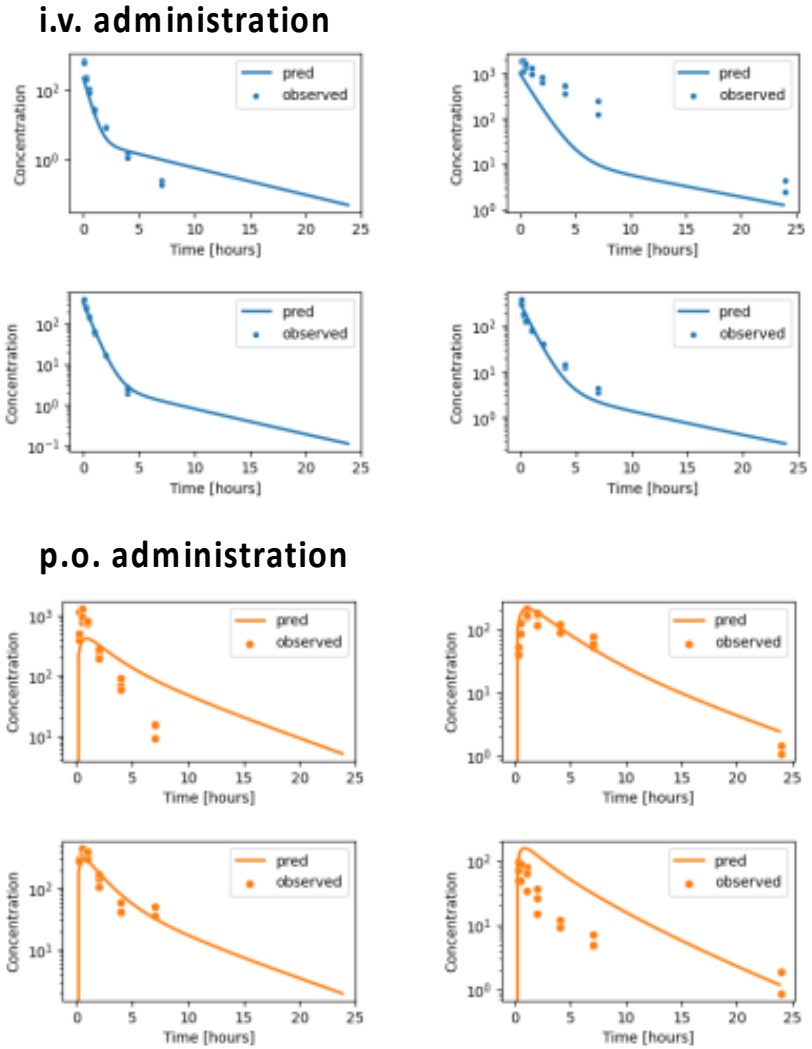
M. Beckers, D. Yonchev, S. Desrayaud, G. Gerebtzoff, R. Rodriguez-Perez. 2024. ChemRxiv

DeepCt: C-t curves' prediction results

- **C-t curves after intravenous (i.v.) and oral (p.o.) administration were predicted for test compounds**

- **AUC i.v., half-life, CL, Vss, and %F are relevant PK parameters that were predicted with median errors < 2-fold**
  - These results are close to experimental variability
  - DeepCt showed equivalent or larger performance than a model that directly predicts PK parameters





*Fold change (FC) = predicted / observed

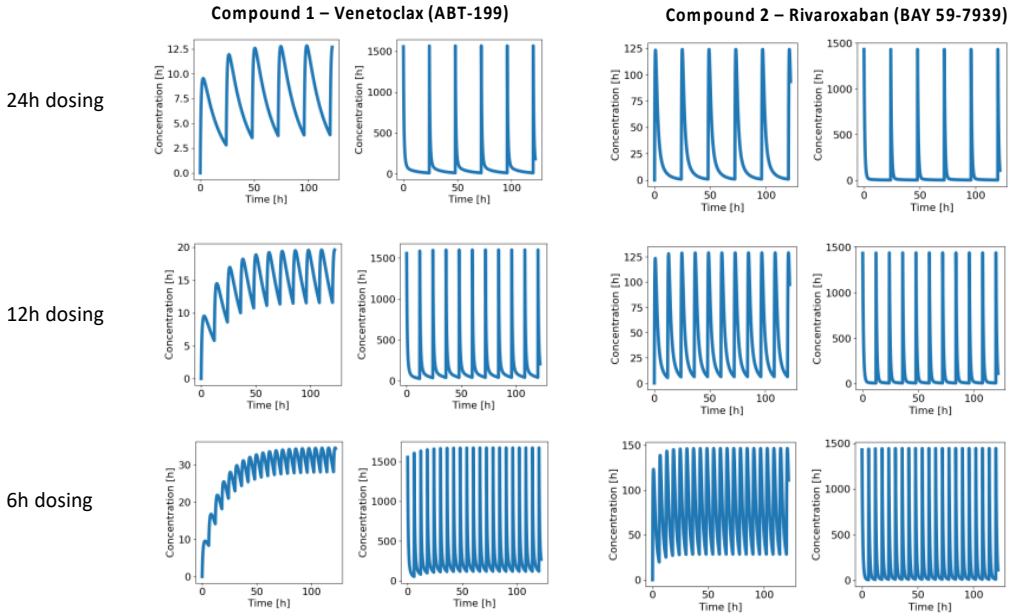
M. Beckers, D. Yonchev, S. Desrayaud, G. Gerebtzoff, R. Rodriguez-Perez. 2024. ChemRxiv

DeepCt: Predicting C-t profiles for multiple dosing regimens

- **DeepCt predicts the constants of a compartmental model, which allows further simulations**

- **Predicted C-t curves are reported for two compounds after both i.v. and p.o. administration after dosing with 1 mg/kg**
  - every 24 hours (top row)
  - every 12 hours (middle row)
  - every 6 hours (bottom row)

- **With C-t profile predictions, we can move towards early in silico PK/PD assessments**



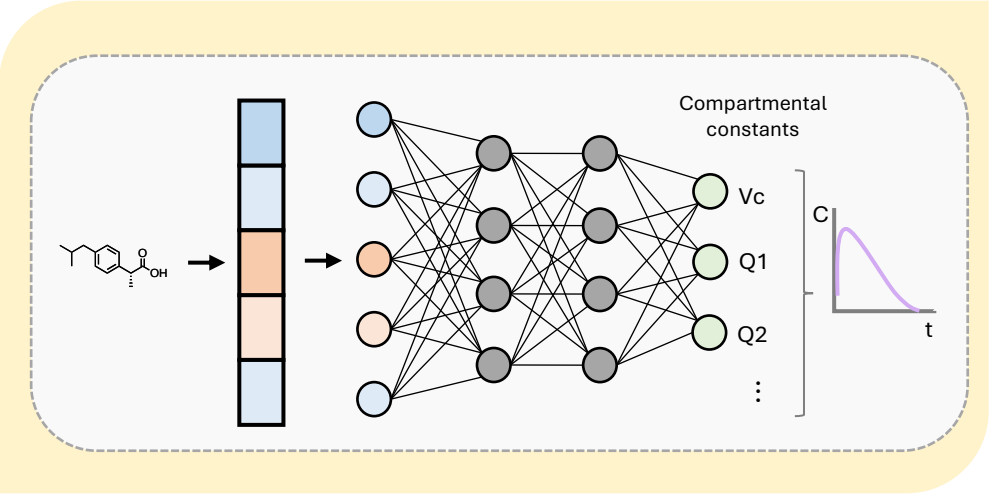
M. Beckers, D. Yonchev, S. Desrayaud, G. Gerebtzoff, R. Rodriguez-Perez. 2024. ChemRxiv

Resources

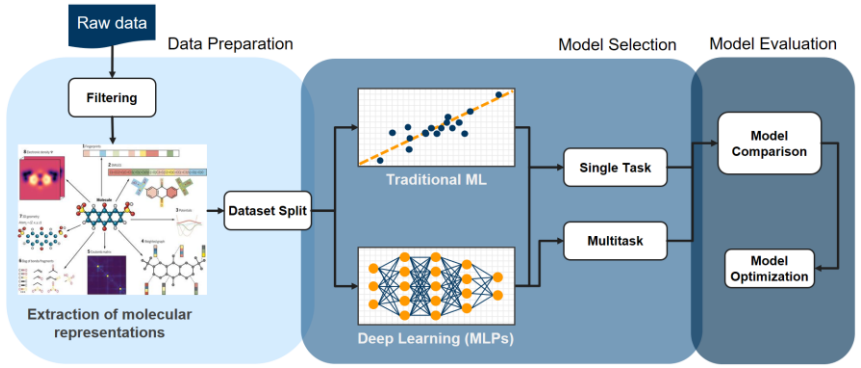
Open-source code

We share code of new methodologies, e.g. DeepCt, as well as libraries or frameworks, e.g. PREFER and UNIQUE

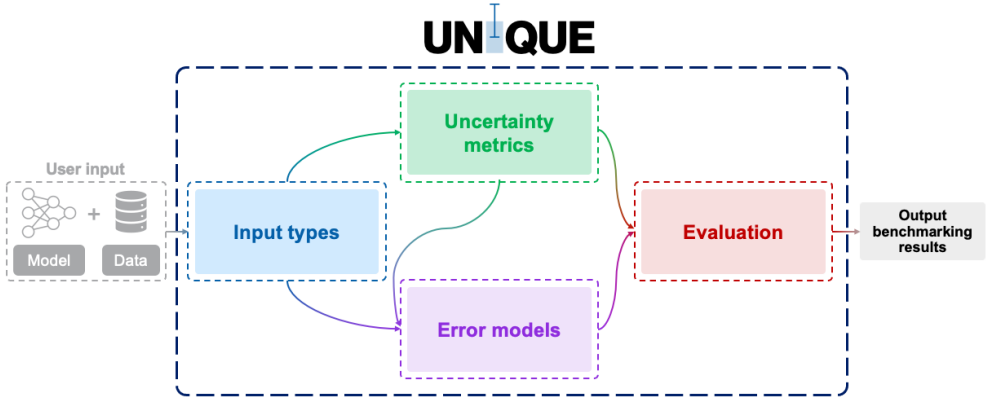
DeepCt: Predicting pharmacokinetic concentration-time curves and compartmental models from chemical structure using deep learning[1]



PREFER framework
(autoML for molecules) [2]



UNIQUE framework
(uncertainty quantification benchmarking) [3]



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[2] J. Lanini et al. JCIM 2023
[3] J. Lanini, M. Huynh, G. Scebba, N. Schneider, R. Rodriguez-Perez, ChemRxiv, 2024

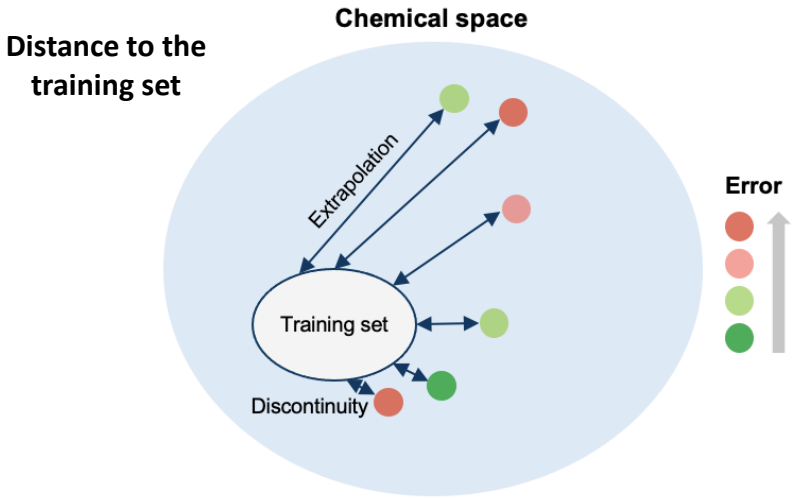
How to quantify uncertainty in ML predictions?

Property models are often evaluated using predictive performance metrics, but it is difficult to evaluate robustness and applicability to individual data points

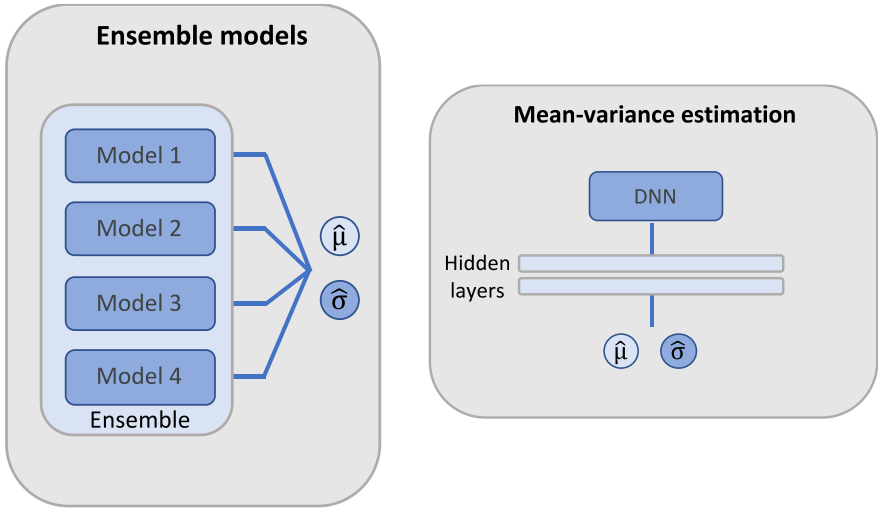
- **When can we trust our model predictions?**

Many uncertainty quantification (UQ) strategies exist, based on the data or the model

Data-based UQ metrics



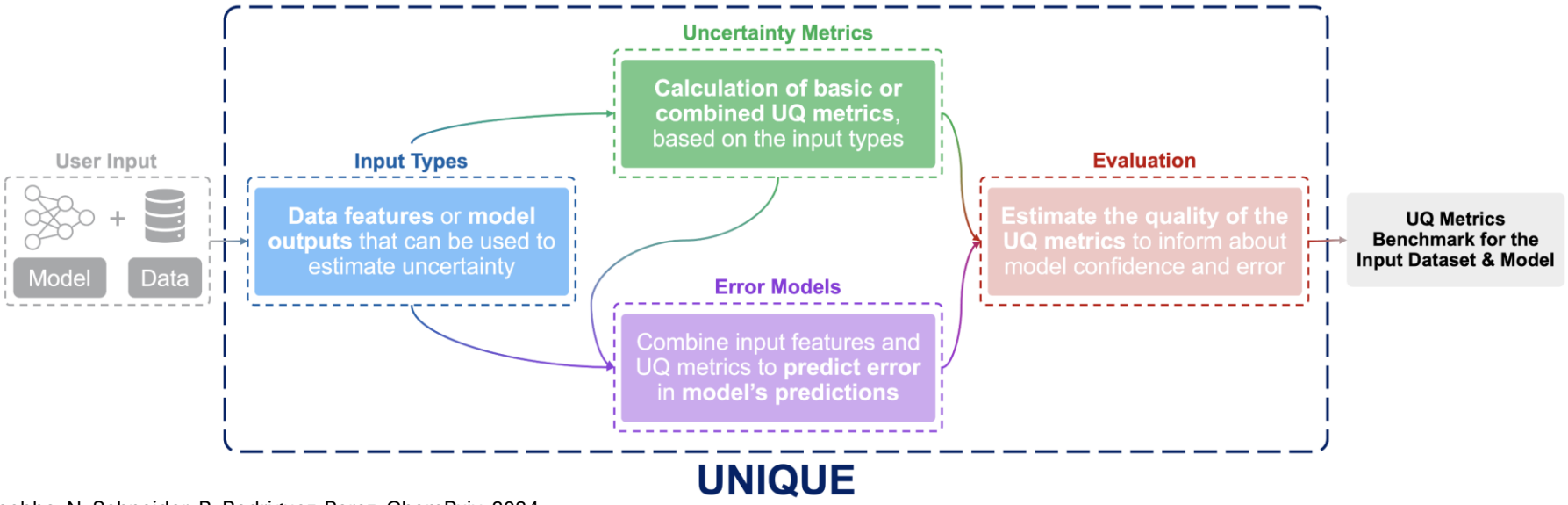
Model-based UQ metrics



Source: F. Miljkovic, R. Rodriguez-Perez, J. Bajorath. ACS Omega. 2021, 6, 49, 33293-33299.

UNIQUE: A Framework for UNcertaInty QUantification bEnchmarking

- Python library that unifies the benchmarking of UQ strategies
- It also includes the calculation of non-standard UQ metrics (combining information from the data and the model)
- Comprehensive evaluation settings are reported to capture the superiority of UQ metrics in different applications scenarios

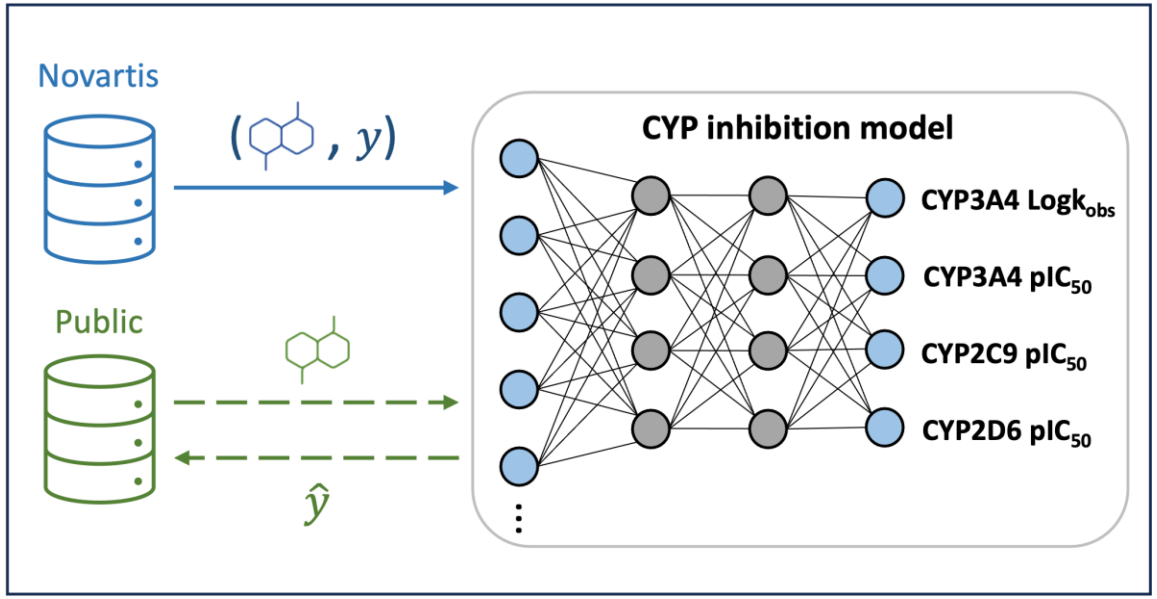


J. Lanini, M. Huynh, G. Scebba, N. Schneider, R. Rodriguez-Perez, ChemRxiv, 2024

Public surrogate data sets

Recently, we have generated ‘surrogate data sets’ and started releasing them open-source

1. **CYP inhibition surrogate data set: 16,373 unique structures from ChEMBL and PubChem databases with annotations of 4 CYP inhibition assays**
2. **ADME surrogate data set with TPDs: ~274,000 structures were obtained from ChEMBL, ZINC, and PROTAC-DB, and annotated with in-house model predictions for 25 properties (assays), such as permeability, lipophilicity, metabolic clearance or solubility**




Chemical Research in Toxicology

Deep Learning Models Compared to Experimental Variability for the Prediction of CYP3A4 Time-Dependent Inhibition

Andrin Fluetsch, Markus Trunzer, Grégori Gerebtzoff, and Raquel Rodríguez-Pérez*


nature communications

Article

Application of machine learning models for property prediction to targeted protein degraders

[1] A. Fluetsch, M. Trunzer, G. Gerebtzoff, R. Rodriguez-Perez Chem. Res. Toxicol. 2024, 37, 4, 549–560
[2] G. Peteani, T. Huynh, G. Gerebtzoff, R. Rodriguez-Perez. Under review

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Thank you!

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