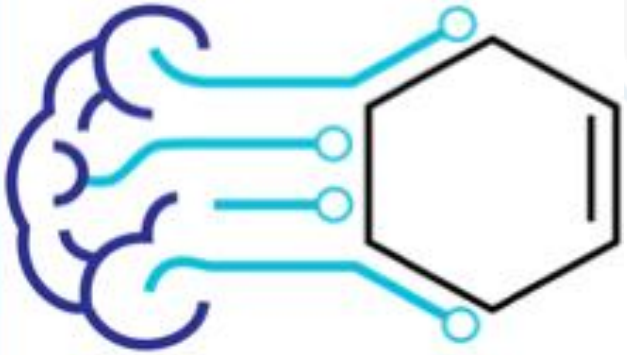
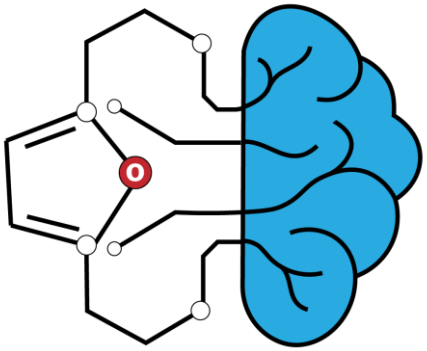




Developing and interpretation of models using OCHEM

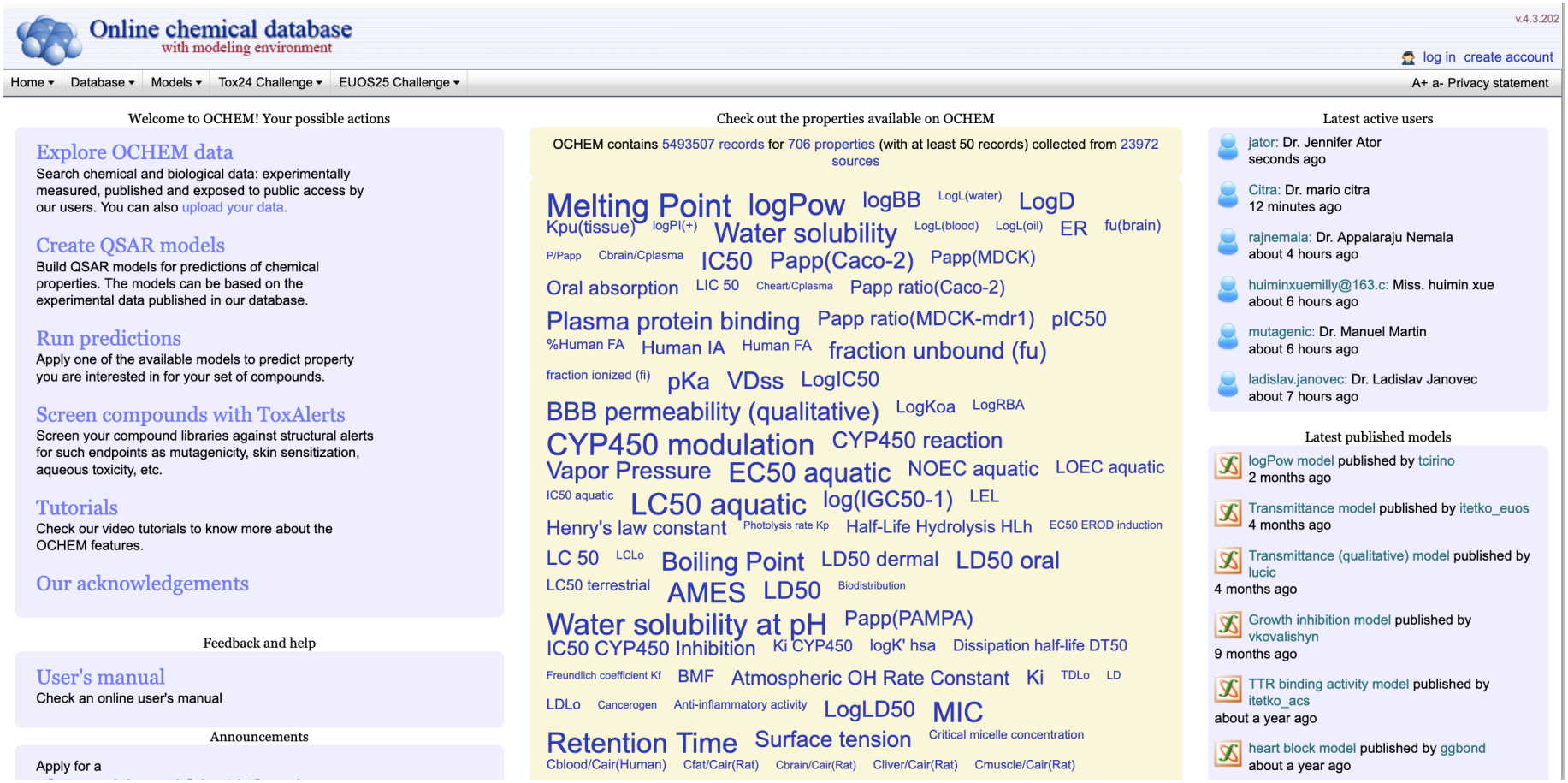
Igor V. Tetko
Institute of Structural Biology, HMGU

19th June 2026

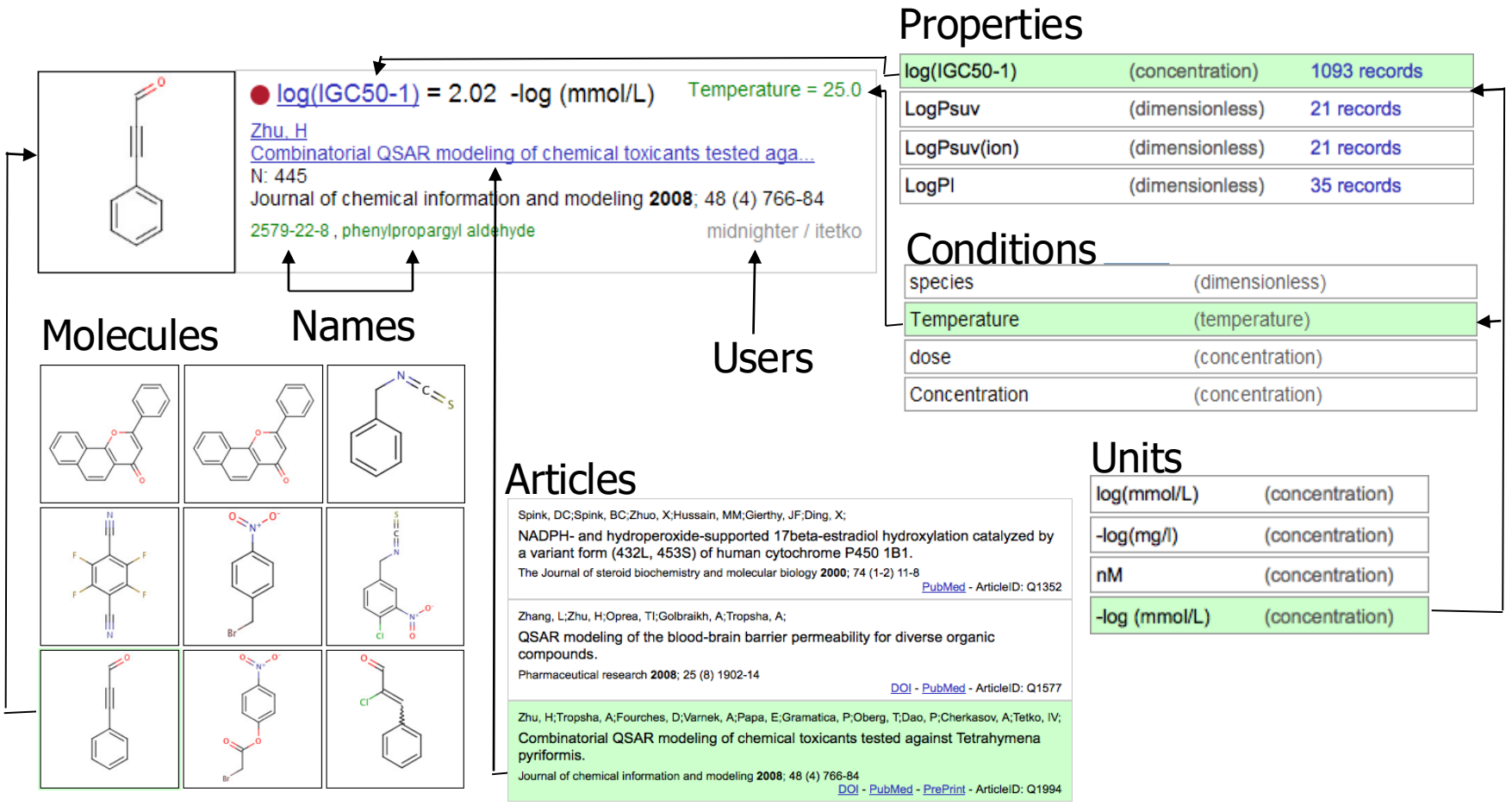
5th AiChemist School on Chemoinformatics

HELMHOLTZ MUNICH

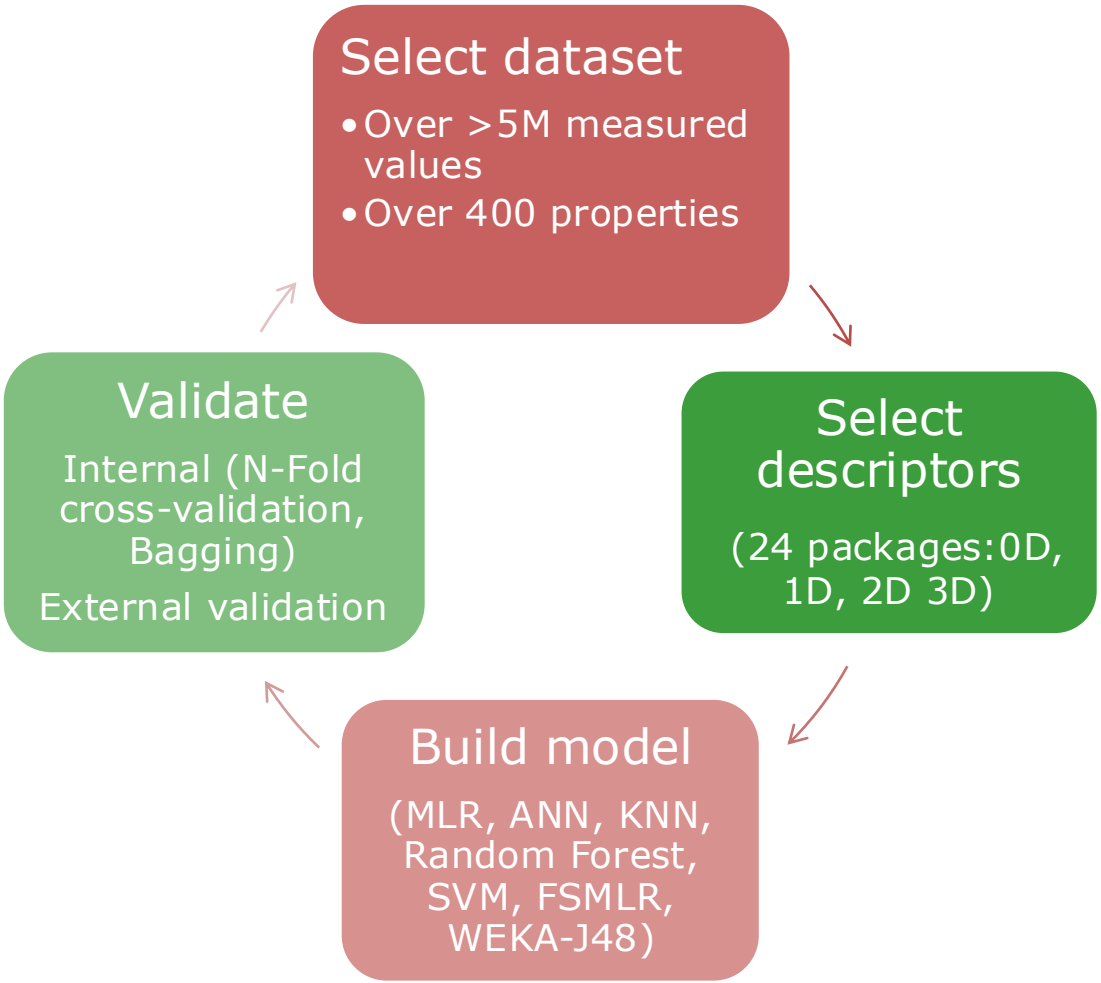
Data storage and model development: https://ochem.eu



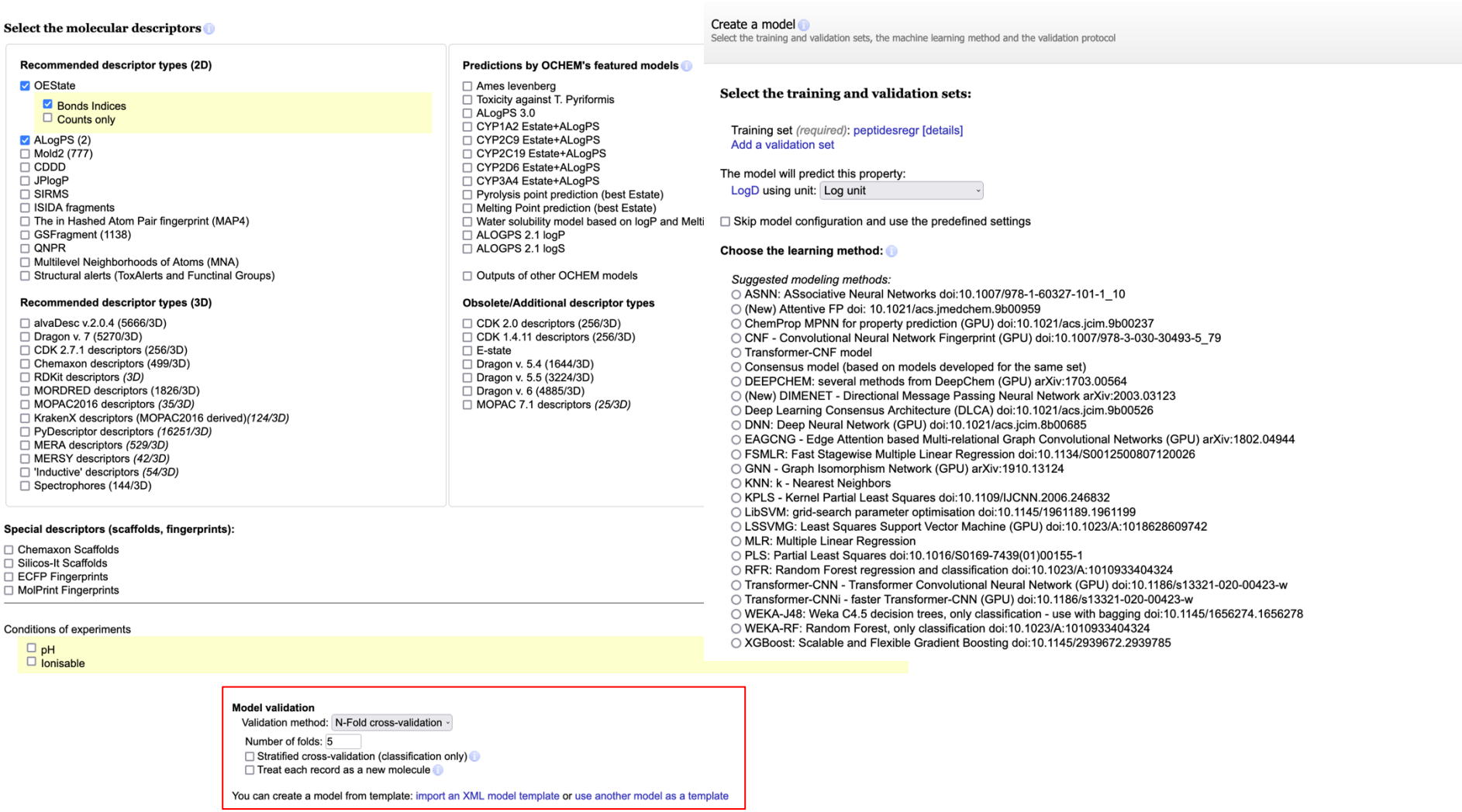
OCHEM Database schema



Modeling iterative workflow



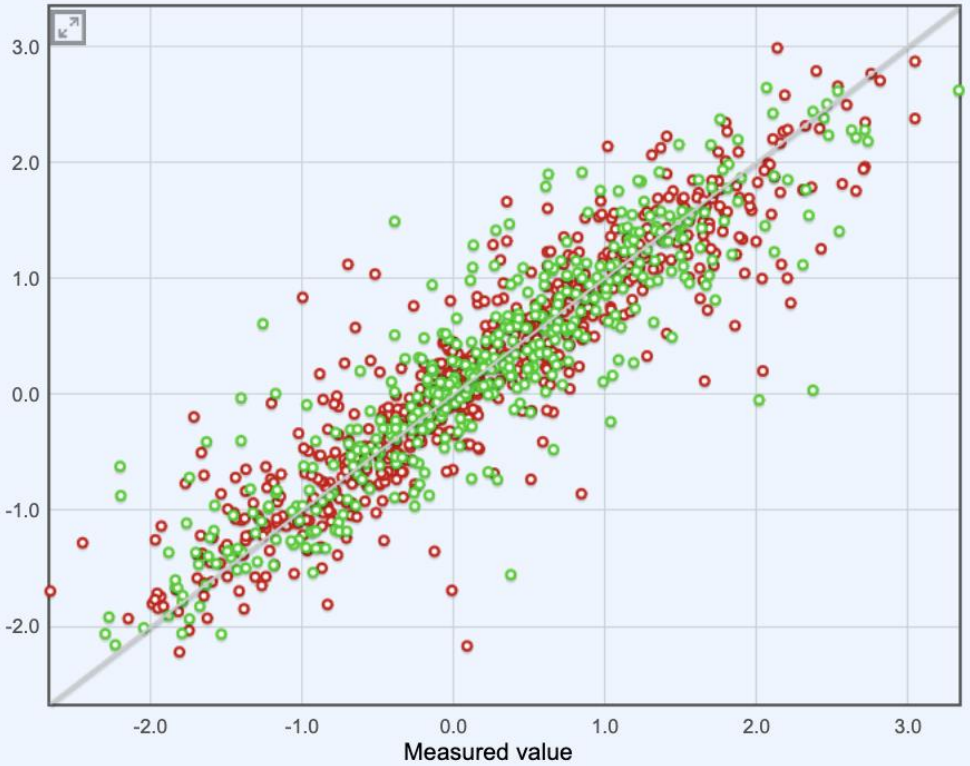
QSPR/QSAR modelling in OCHEM



Confidence intervals

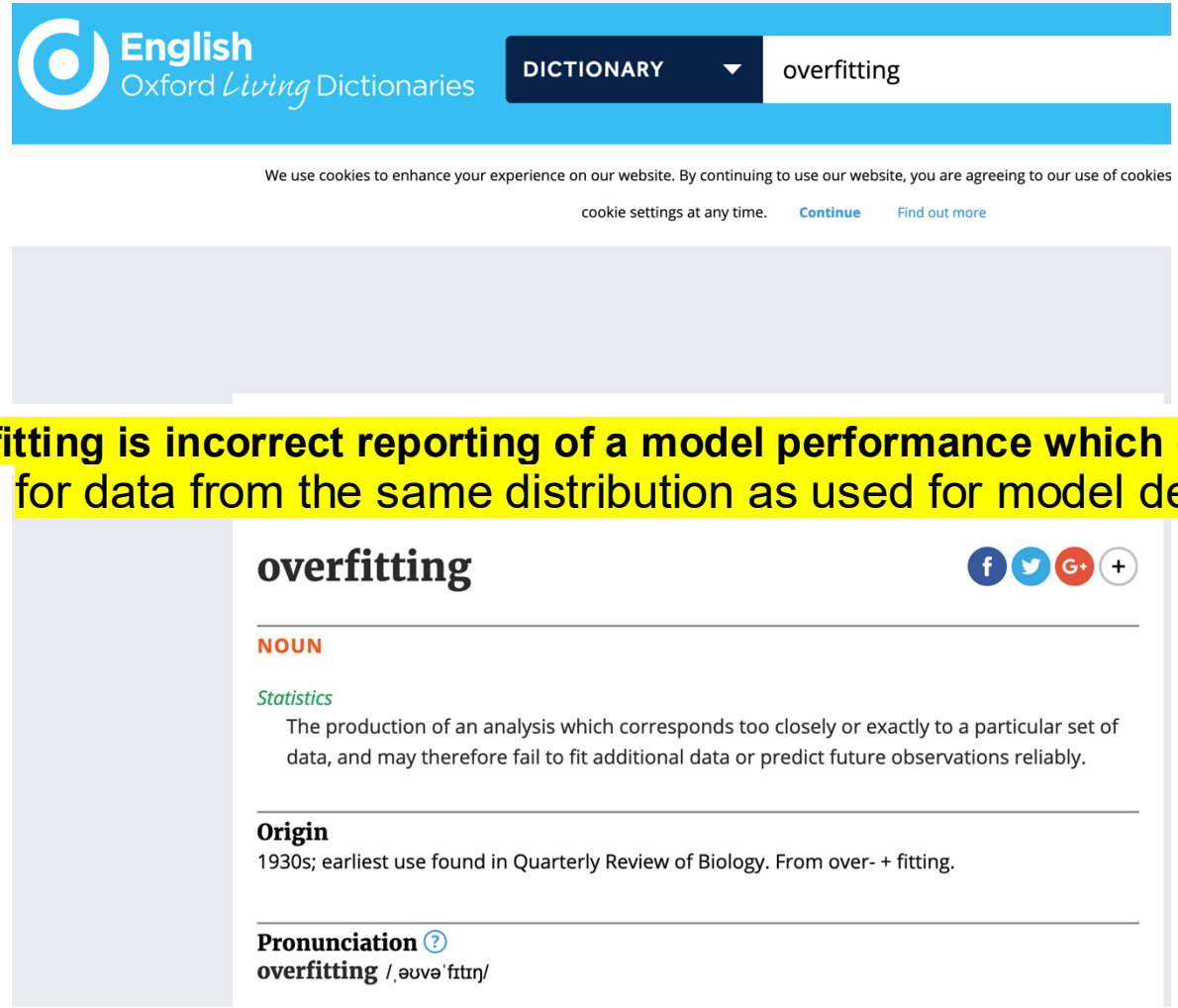
Predicted property: **log(IGC50-1)** modeled in -log(mmol/L)
Training method: ASNN

Data Set	#	R2	q2	RMSE	MAE
Training set: T. pyriformis (training)	644 records	0.83 ± 0.02	0.83 ± 0.02	0.44 ± 0.02	0.31 ± 0.01
Test set: T. pyriformis (test) [x]	449 records	0.81 ± 0.02	0.8 ± 0.02	0.46 ± 0.03	0.32 ± 0.02



Overfitting

Overfitting



Overfitting is incorrect reporting of a model performance which overestimates for data from the same distribution as used for model development.

https://en.oxforddictionaries.com/definition/overfitting

Examples of overfitting by neural networks

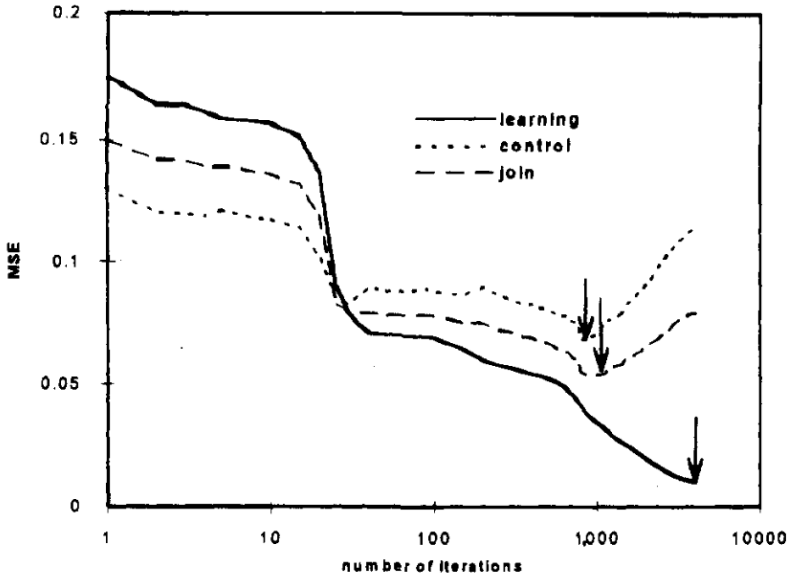
J. Chem. Inf. Comput. Sci. **1995,** *35,* 826−833

Neural Network Studies. 1. Comparison of Overfitting and Overtraining

Igor V. Tetko,† David J. Livingstone,‡,§ and Alexander I. Luik*,†

Biomedical Department, Institute of Bioorganic and Petroleum Chemistry, Murmanskaya, 1, Kiev-660, 253660, Ukraine, ChemQuest, Cheyney House, 19-21 Cheyney Street, Steeple Morden, Herts, SG8 0LP, U.K., and Centre for Molecular Design, University of Portsmouth, Portsmouth, Hants, PO1 2EG, U.K.

Received January 27, 1995®

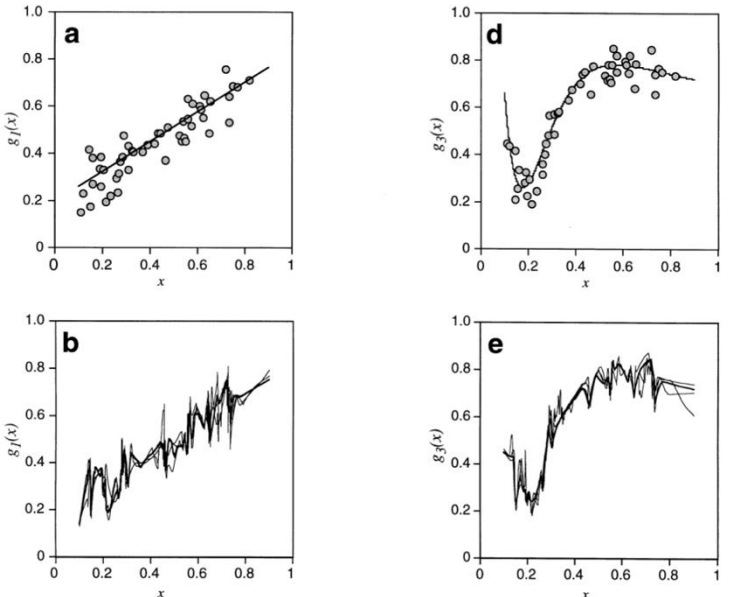


Neural Processing Letters **6:** 43–50, 1997.

An Enhancement of Generalization Ability in Cascade Correlation Algorithm by Avoidance of Overfitting/Overtraining Problem

IGOR V. TETKO[1,2] and ALESSANDRO E.P. VILLA[1]
[1] *Laboratoire de Neuro-heuristique, Institut de Physiologie, Université de Lausanne, Rue du Bugnon 7, Lausanne, CH–1005, Switzerland;* [2] *Department of Biomedical Applications, Institute of Bioorganic and Petroleum Chemistry, Murmanskaya, 1, Kiev–660, 253660, Ukraine*
E-mail: Alessandro.Villa@iphysiol.unil.ch

Key words: cascade correlation algorithm, early stopping, overfitting, overtraining



Examples of overfitting by neural networks

Neural Processing Letters **6:** 43–50, 1997.

An Enhancement of Generalization Ability in Cascade Correlation Algorithm by Avoida Overfitting/Overtraining Problem

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E-mail: Alessandro.Villa@iphysiol.unil.ch

Key words: cascade correlation algorithm, early stopping, overfitting, overtraining

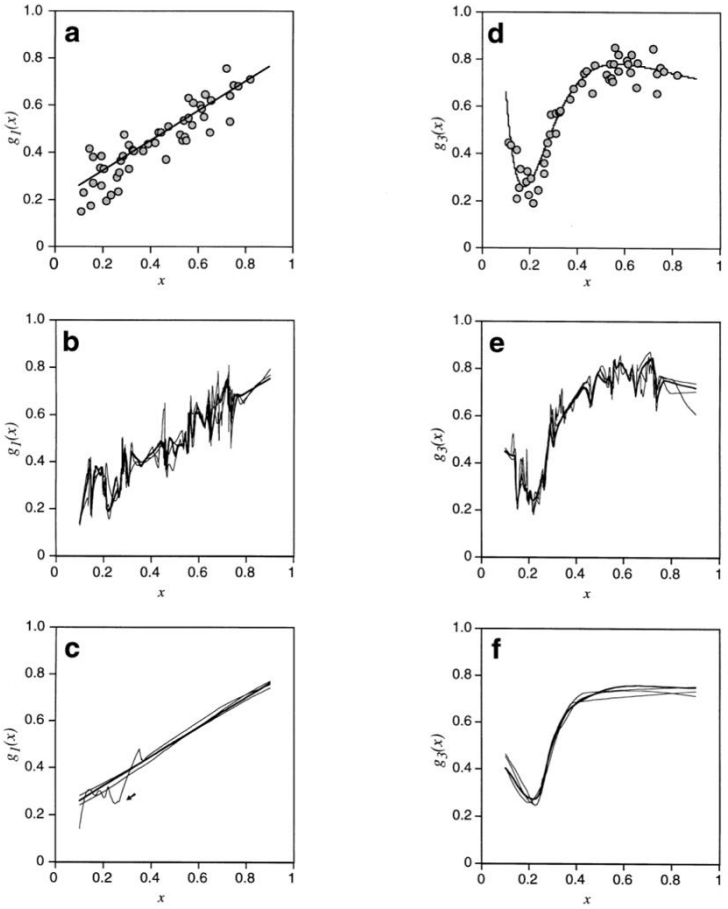


Figure 1. Training Data sets and Calculated Curves

Panels **[a-c]** refer to function $g_1(x)$ and panels **[d-f]** refer to function $g_3(x)$.
[a], [d]: circles represent 50 cases of the training data set and the thick line represent the function $g(x)$ over the interval [0.1,0.9].
[b], [e]: three examples of overtrained ANNs (thin lines) and an ensemble average of 100 such ANNs (thick lines);
[c], [f]: three examples of early stopping ANNs (thin lines) and an ensemble average of 100 such ANNs (thick lines).

Overfitting by variable selection: Simulated Dataset

N = 74 molecules (Boiling point of alkenes)

100 random variables

Software WEKA:

k-nearest neighbors

MLR (Multiple Linear Rgression)

Tutorial on Machine Learning. Part 2. Descriptor Selection Bias.
Conference: The Strasbourg Summer School on Chemoinformatics (1st Chemoinformatics Strasbourg Summer School)
DOI:10.13140/RG.2.2.26353.43361

Cross-validation strategies

A. Descriptors (+ model hyperparameters) are selected using the whole set (training + validation set); CV is done after selection

B. Descriptors and model are selected when estimating errors on the validation set; CV results are reported for the model optimized on the respective validation fold

C. Validation set is kept hidden, descriptors (and model) are selected using respective training set

Selection of descriptors and hyperparameter optimization of model can be done using any available method.

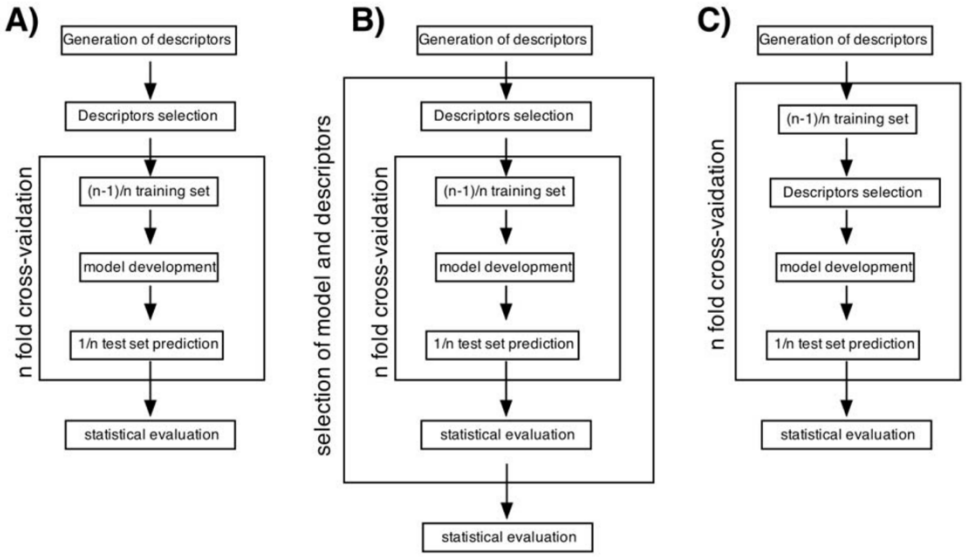


Figure 1. Internal (A, B) and External (C) cross-validation procedures.

Comparison of validation performances

Strategy A: correlation coefficient, R = 0.82

RMSE = 27 ° C

Strategy B: R = 0.55

RMSE = 39 ° C

Strategy C: R = -0.28

RMSE = 54 ° C ~ random

Strategy C – double or nested cross-validation; recommended!

The use of incorrect validation (strategy 1-2) contributes overfitting!

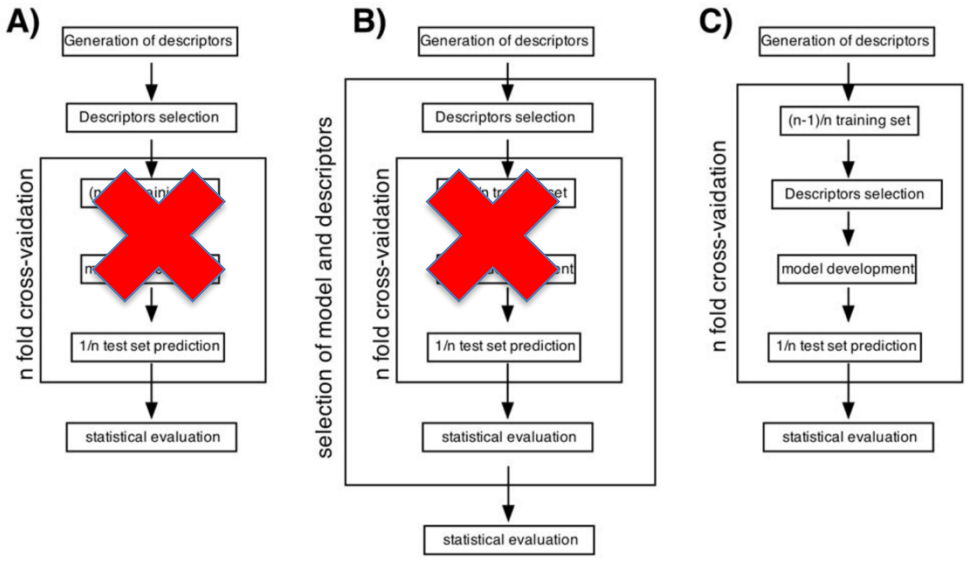
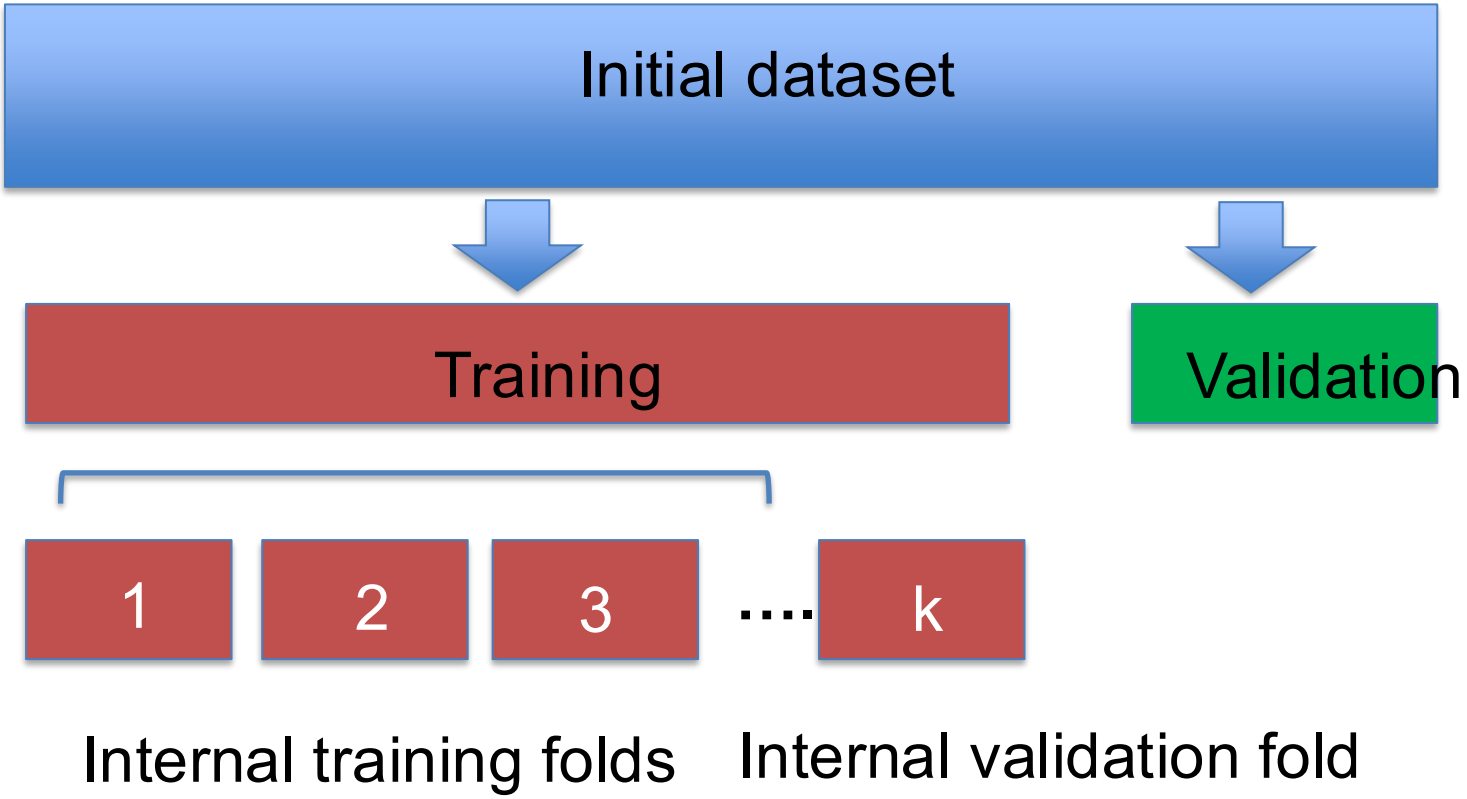


Figure 1. Internal (A, B) and External (C) cross-validation procedures.

Strategy C: Double cross-validation



But… is it always required?

scientific **data**

OPEN

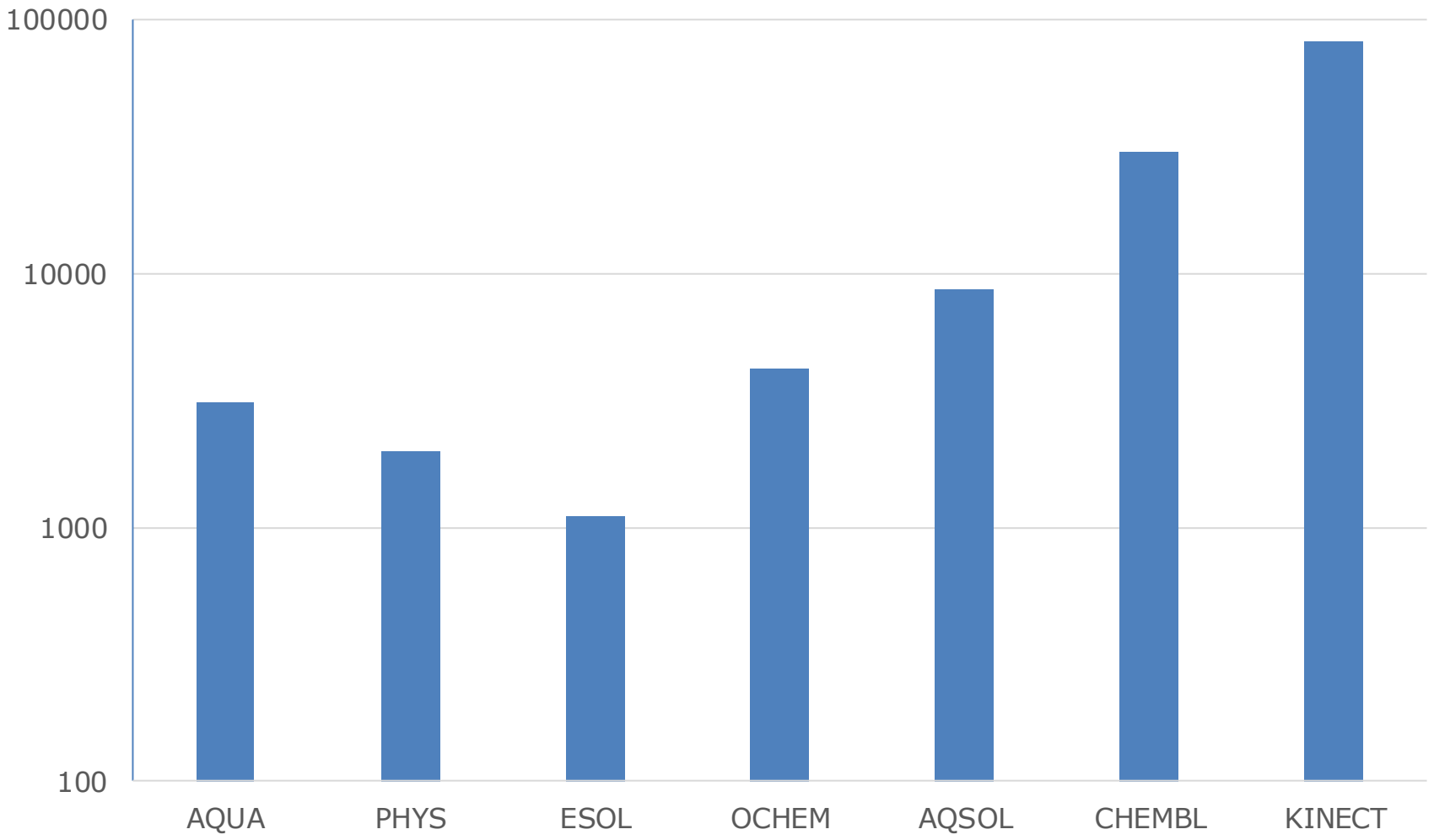
ANALYSIS

Boosting the predictive performance with aqueous solubility dataset curation

Jintao Meng[1,5,6], Peng Chen[2,3]✉, Mohamed Wahib[2,3], Mingjun Yang[4], Liangzhen Zheng[1], Yanjie Wei[1]✉, Shengzhong Feng[5]✉ & Wei Liu[6]

Intrinsic solubility is a critical property in pharmaceutical industry that impacts *in-vivo* bioavailability of small molecule drugs. However, solubility prediction with Artificial Intelligence(AI) are facing insufficient data, poor data quality, and no unified measurements for AI and physics-based approaches. We collect 7 aqueous solubility datasets, and present a dataset curation workflow. Evaluating the curated data with two expanded deep learning methods, improved RMSE scores on all curated thermodynamic datasets are observed. We also compare expanded *Chemprop* enhanced with curated data and state-of-art physics-based approach using pearson and spearman correlation coefficients. A similar performance on pearson with 0.930 and spearman with 0.947 from expanded *Chemprop* is achieved. A steadily improved pearson and spearman values with increasing data points are also illustrated. Besides that, the computation advantage of AI models enables quick evaluation of a large set of molecules during the hit identification or lead optimization stages, which helps further decision making within the time cycle at drug discovery stage.

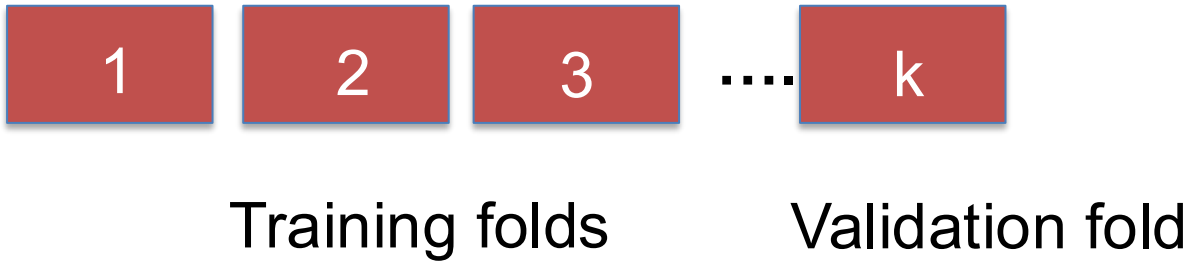
Data setup


100000
10000
1000
100
AQUA
PHYS
ESOL
OCHEM
AQSOL
CHEMBL
KINECT

Modellling approach

Grid hyperparameter optimization on each step – 108 combinations of parameters; the lowest RMSE is stored.

- Hidden neurons size, depth, dropout, number of feed-forward layers.
- Hyperparameter optimization script sees all the data given to it.
- Use of ensemble of 5 models to improve the model accuracy.
- Use 8 repetitions to obtain confidence intervals.
- Two weeks using 1200 compute nodes (38,200 cores and 4800 GPU accelerators)
- https://github.com/Mengjintao/chemprop

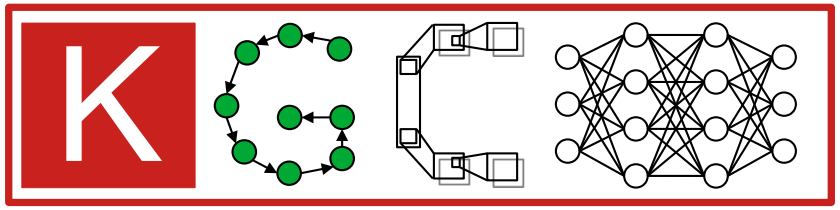


openOCHEM GitHub

Implementation:

https://github.com/openochem/openochem

https://solub.ochem.eu



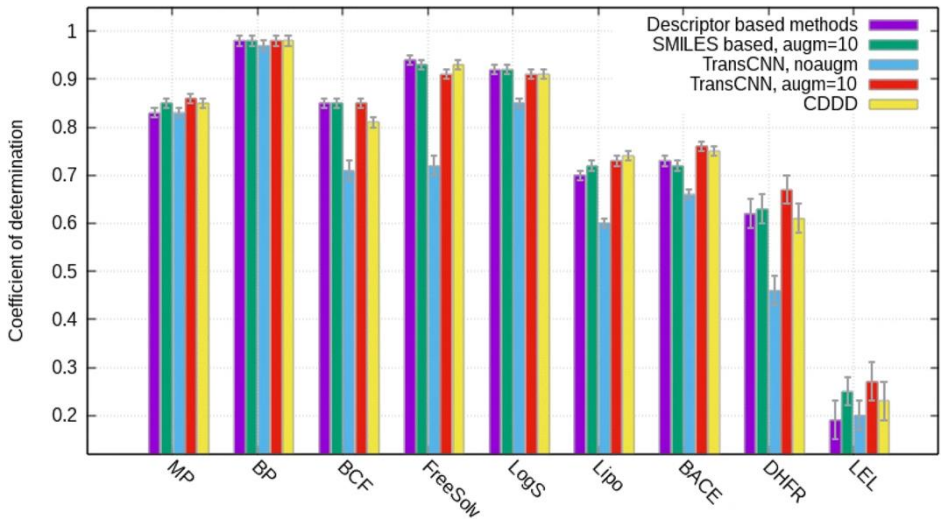
KGCNN

https://github.com/aimat-lab/gcnn_keras

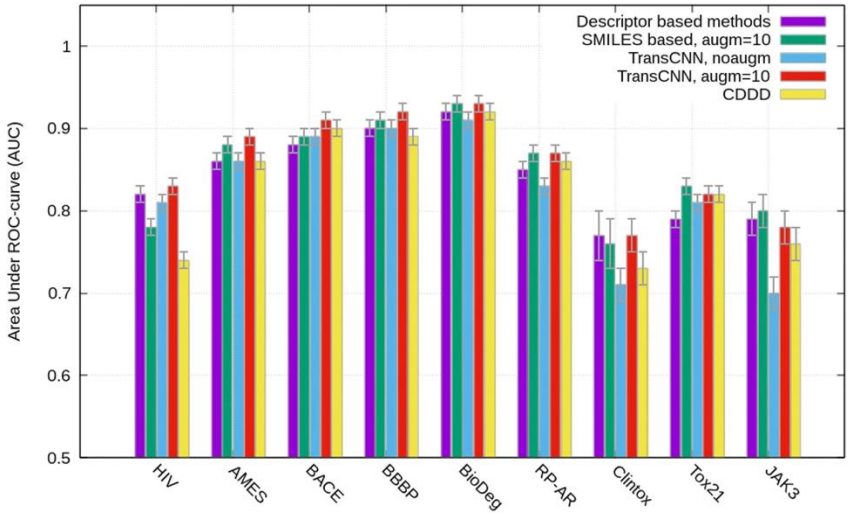
Reiser, P.; Eberhard, A.; Friederich, P. Graph Neural Networks in TensorFlow-Keras with RaggedTensor Representation (Kgcnn). *Softw. Impacts* **2021**, *9*, 100095. https://doi.org/10.1016/j.simpa.2021.100095.

Hypeparameter pre-optimisation

Regression tasks



Classification tasks



Tetko, I. V.; Karpov, P.; Bruno, E.; Kimber, T. B.; Godin, G. Augmentation Is What You Need! In *Artificial Neural Networks and Machine Learning – ICANN 2019: Workshop and Special Sessions*; Tetko, I. V., Kůrková, V., Karpov, P., Theis, F., Eds.; Lecture Notes in Computer Science; Springer International Publishing: Cham, 2019; pp 831–835. https://doi.org/10.1007/978-3-030-30493-5_79 .

Karpov, P.; Godin, G.; Tetko, I. V. Transformer-CNN: Swiss Knife for QSAR Modeling and Interpretation. J. Cheminformatics 2020, 12 (1), 17. https://doi.org/10.1186/s13321-020-00423-w.

Comparison of Root Mean Squared Errors (RMSE) based on tuned and pre-set hyper-parameters („Org“ sets)

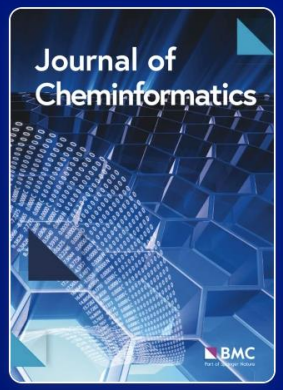
Dataset	Published by Meng at al (following hyperparameters optimisation)		Results from this study (using default hyperparameters of methods)		
			RMSE, validation by molecule		
	ChemProp	AttFP	ChemProp	AttFP	Transformer CNN
AQUA	0.58 ± 0.04	0.62 ± 0.03	0.58 ± 0.02	**0.60 ± 0.02**	0.56 ± 0.02*
PHYSP	**0.55 ± 0.03**	0.65 ± 0.02	0.57 ± 0.01	**0.59 ± 0.01**	0.56 ± 0.01*
ESOL	**0.60 ± 0.08**	0.64 ± 0.02	0.61 ± 0.01	**0.59 ± 0.02**	0.58 ± 0.02*
OCHEM	**0.55 ± 0.02**	**0.60 ± 0.01**	0.63 ± 0.01	0.65 ± 0.01	0.59 ± 0.01**
AQSOL	1.02 ± 0.04	**0.83 ± 0.03**	**1. ± 0.02**	1.01 ± 0.02	0.99 ± 0.01*
CHEMBL	0.92 ± 0.02	n/a	**0.88 ± 0.01**	0.93 ± 0.01	0.86 ± 0.01**
KINECT	**0.401 ± 0.001**	n/a	0.434 ± 0.002	0.465 ± 0.001	0.41 ± 0.002**

Pre-set hyperparameters provided better performance in 18 of 34 pairwise comparisons (and ca 10000x faster!)

Be aware of overfitting by hyperparameter optimization!

Research | Open access | Published: 09 December 2024

Volume 16, article number 139 (2024) Cite this article



Igor V. Tetko, Ruud van Deursen & Guillaume Godin

Using power of OCHEM tools

Comprehensive modelling

Comprehensive modelling

Comprehensive modelling

Predicted property: log(IGC50-1)
Training set: T. pyriformis (training)
Duplicate models: start

Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (32

	ASNN (CHEMAXON)	DNN	Represent.
ALogPS, OEstate	+	0.53	+
ALogPS, StructuralAlerts	+	0.48	+
CDDD	+	0.5	+
CDK23 (cons,topol,geom,elect,hybr) 3D:rdkit3d	+	0.52	+
Dragon6 (2D blocks: 1 28)	+	0.7	+
Dragon7 (3D blocks: 1-30) 3D:rdkit3d	+	0.51	+
EPA (T.E.S.T.)	+	0.51	+
Fragmentor (length: 2-4)	+	0.48	+
GSFrag (F + L)	+	0.62	+
InductiveDescriptors 3D:rdkit3d	+	0.51	+
JPlogP	+	0.51	+
MNA	+	0.79	+
MOLD2	+	0.52	+
MORDRED (2D)	+	0.53	+
MORDRED (3D) 3D:rdkit3d	+	0.56	+
OEstate	0.44 (+1 models)	0.48	+
OSMORDRED	+	0.51	+
QNPR (length:1 - 3)	+	0.58	+
RDKIT (2D blocks: 1-3 5 10-11 15-16)	+	0.6	+
RDKIT (3D blocks: 1-11 15-16) 3D:rdkit3d	+	0.56	+
RDKIT (ECFP4)	+	0.85	+
SIRMS (labels: charge+logp+hb+refractivity)	+	0.54	+
alvaDesc (2D blocks: 1-12 22-25 29 32-33)	+	0.54	+
alvaDesc (3D blocks: 1-33) 3D:rdkit3d	+	0.54	+
CNF2 (F) (3D) 10/10	+	+	0.46
DEEPCHEM (F) (3D) TEXTCNN 10/10	+	+	0.47
KGCNN AttFP	+	+	0.42
KGCNN ChemProp	+	+	0.43
TRANSNN (F) (3D) 10/10	+	+	0.52
TRANSNNI (F) 10/10	+	+	0.43

Predicted property: log(IGC50-1)
Training set: T. pyriformis (training)
Duplicate models: start

Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (32

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Dragon7 (3D blocks: 1-30) 3D:rdkit3d	+	0.51	+
EPA (T.E.S.T.)	+	0.51	+
Fragmentor (length: 2-4)	+	0.48	+
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SIRMS (labels: charge+logp+hb+refractivity)	+	0.54	+
alvaDesc (2D blocks: 1-12 22-25 29 32-33)	+	0.54	+
alvaDesc (3D blocks: 1-33) 3D:rdkit3d	+	0.54	+
CNF2 (F) (3D) 10/10	+	+	0.46
DEEPCHEM (F) (3D) TEXTCNN 10/10	+	+	0.47
KGCNN AttFP	+	+	0.42
KGCNN ChemProp	+	+	0.43
TRANSNN (F) (3D) 10/10	+	+	0.52
TRANSNNI (F) 10/10	+	+	0.43

Comprehensive modelling

Predicted property: log(IGC50-1)
Training set: T. pyriformis (training)
Duplicate models: start

Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (41 models)

	ASNN (CHEMAXON)	DNN	Represent.	FSMLR	KNN	MLRA	PLS	LSSVMG	XGBOOST	RFR	SCI:CAT_BOOST
ALogPS, OEstate	+	0.53	+	+	+	+	+	+	+	+	+
ALogPS, StructuralAlerts	+	0.48	+	+	+	+	+	+	+	+	+
CDDD	+	0.5	+	+	+	+	+	+	+	+	+
CDK23 (cons,topol,geom,elect,hybr) 3D:rdkit3d	+	0.52	+	+	+	+	+	+	+	+	+
Dragon6 (2D blocks: 1 28)	+	0.7	+	+	+	+	+	+	+	+	+
Dragon7 (3D blocks: 1-30) 3D:rdkit3d	+	0.51	+	+	+	+	+	+	+	+	+
EPA (T.E.S.T.)	+	0.51	+	+	+	+	+	+	+	+	+
Fragmentor (length: 2-4)	running	0.48	+	0.48	0.67	0.59	0.49	0.62	0.51	0.5	0.43
GSFrag (F + L)	+	0.62	+	+	+	+	+	+	+	+	+
InductiveDescriptors 3D:rdkit3d	+	0.51	+	+	+	+	+	+	+	+	+
JPlogP	+	0.51	+	+	+	+	+	+	+	+	+
MNA	+	0.79	+	+	+	+	+	+	+	+	+
MOLD2	+	0.52	+	+	+	+	+	+	+	+	+
MORDRED (2D)	+	0.53	+	+	+	+	+	+	+	+	+
MORDRED (3D) 3D:rdkit3d	+	0.56	+	+	+	+	+	+	+	+	+
OEstate	0.44 (+1 models)	0.48	+	+	+	+	+	+	+	+	+
OSMORDRED	+	0.51	+	+	+	+	+	+	+	+	+
QNPR (length:1 - 3)	+	0.58	+	+	+	+	+	+	+	+	+
RDKIT (2D blocks: 1-3 5 10-11 15-16)	+	0.6	+	+	+	+	+	+	+	+	+
RDKIT (3D blocks: 1-11 15-16) 3D:rdkit3d	+	0.56	+	+	+	+	+	+	+	+	+
RDKIT (ECFP4)	+	0.85	+	+	+	+	+	+	+	+	+
SIRMS (labels: charge+logp+hb+refractivity)	+	0.54	+	+	+	+	+	+	+	+	+
alvaDesc (2D blocks: 1-12 22-25 29 32-33)	+	0.54	+	+	+	+	+	+	+	+	+
alvaDesc (3D blocks: 1-33) 3D:rdkit3d	+	0.54	+	+	+	+	+	+	+	+	+
CNF2 (F) (3D) 10/10	+	+	0.46	+	+	+	+	+	+	+	+
DEEPCHEM (F) (3D) TEXTCNN 10/10	+	+	0.47	+	+	+	+	+	+	+	+
KGCNN AttFP	+	+	0.42	+	+	+	+	+	+	+	+
KGCNN ChemProp	+	+	0.43	+	+	+	+	+	+	+	+
TRANSNN (F) (3D) 10/10	+	+	0.52	+	+	+	+	+	+	+	+
TRANSNNI (F) 10/10	+	+	0.43	+	+	+	+	+	+	+	+

Delete 1 matching models
Create 29 missing models
Create models for those saved in the first column

Comprehensive modelling

Predicted property: log(IGC50-1)
Training set: T. pyriformis (training)
Duplicate models: start

Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (78 models)

	ASNN (CHEMAXON)	DNN	Represent.	FSMLR	KNN	MLRA	PLS	LSSVMG	XGBOOST	RFR	SCI:CAT_BOOST
ALogPS, OEstate	+	0.53	+	+	+	+	+	+	+	+	0.42
ALogPS, StructuralAlerts	0.42	0.48	+	0.52	0.6	0.56	0.49	0.56	0.46	0.45	0.43
CDDD	+	0.5	+	+	+	+	+	+	+	+	0.55
CDK23 (cons,topol,geom,elect,hybr) 3D:rdkit3d	+	0.52	+	+	+	+	+	+	+	+	0.47
Dragon6 (2D blocks: 1 28)	+	0.7	+	+	+	+	+	+	+	+	0.76
Dragon7 (3D blocks: 1-30) 3D:rdkit3d	+	0.51	+	+	+	+	+	+	+	+	0.49
EPA (T.E.S.T.)	+	0.51	+	+	+	+	+	+	+	+	0.46
Fragmentor (length: 2-4)	running	0.48	+	0.48	0.67	0.59	0.49	0.62	0.51	0.5	0.43
GSFrag (F + L)	+	0.62	+	+	+	+	+	+	+	+	0.57
InductiveDescriptors 3D:rdkit3d	+	0.51	+	+	+	+	+	+	+	+	0.55
JPlogP	+	0.51	+	+	+	+	+	+	+	+	0.46
MNA	+	0.79	+	+	+	+	+	+	+	+	0.64
MOLD2	+	0.52	+	+	+	+	+	+	+	+	0.48
MORDRED (2D)	+	0.53	+	+	+	+	+	+	+	+	0.49
MORDRED (3D) 3D:rdkit3d	+	0.56	+	+	+	+	+	+	+	+	0.49
OEstate	0.44	0.48	+	0.54	0.6	0.93	0.51	0.54	0.54	0.5	0.45
OSMORDRED	+	0.51	+	+	+	+	+	+	+	+	0.48
QNPR (length:1 - 3)	+	0.58	+	+	+	+	+	+	+	+	0.5
RDKIT (2D blocks: 1-3 5 10-11 15-16)	+	0.6	+	+	+	+	+	+	+	+	0.47
RDKIT (3D blocks: 1-11 15-16) 3D:rdkit3d	+	0.56	+	+	+	+	+	+	+	+	0.5
RDKIT (ECFP4)	+	0.85	+	+	+	+	+	+	+	+	0.64
SIRMS (labels: charge+logp+hb+refractivity)	+	0.54	+	+	+	+	+	+	+	+	0.43
alvaDesc (2D blocks: 1-12 22-25 29 32-33)	+	0.54	+	+	+	+	+	+	+	+	0.48
alvaDesc (3D blocks: 1-33) 3D:rdkit3d	+	0.54	+	+	+	+	+	+	+	+	0.49
CNF2 (F) (3D) 10/10	+	+	0.46	+	+	+	+	+	+	+	+
DEEPCHEM (F) (3D) TEXTCNN 10/10	+	+	0.47	+	+	+	+	+	+	+	+
KGCNN AttFP	+	+	0.42	+	+	+	+	+	+	+	+
KGCNN ChemProp	+	+	0.43	+	+	+	+	+	+	+	+
TRANSNN (F) (3D) 10/10	+	+	0.52	+	+	+	+	+	+	+	+
TRANSNNI (F) 10/10	+	+	0.43	+	+	+	+	+	+	+	+

Selection of best models

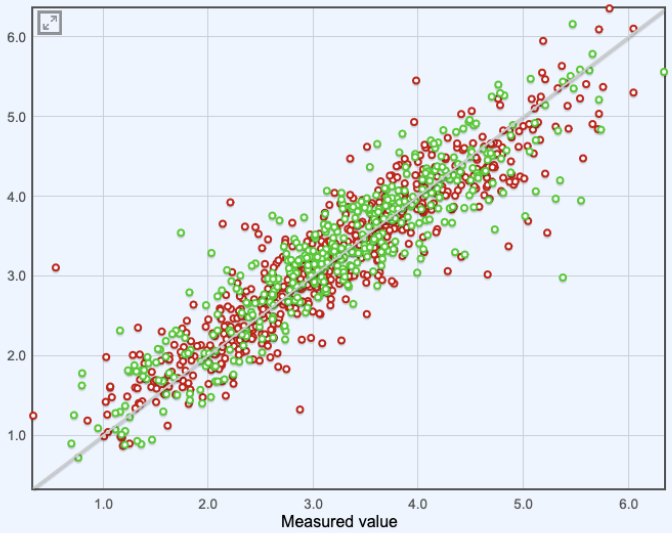
Model profile
Statistical parameters, tables, charts - all the information related to the model.

Overview | Applicability domain

Model name: log(IGC50-1)_KGCNN AttFP [rename]
Temporal Public ID: 22966388 - use this link to share this temporal model (will be deleted after 3 months unless published)

Predicted property: **log(IGC50-1)** modeled in -log(mol/L)
Training method: KGCNN

Data Set	#	R_2	q_2	RMSE	MAE
Training set: T. pyriformis (training)	644 records	0.84 ± 0.01	0.84 ± 0.01	0.42 ± 0.02	0.3 ± 0.01
Test set: T. pyriformis (test) [x]	449 records	0.83 ± 0.02	0.83 ± 0.02	0.44 ± 0.02	0.33 ± 0.01

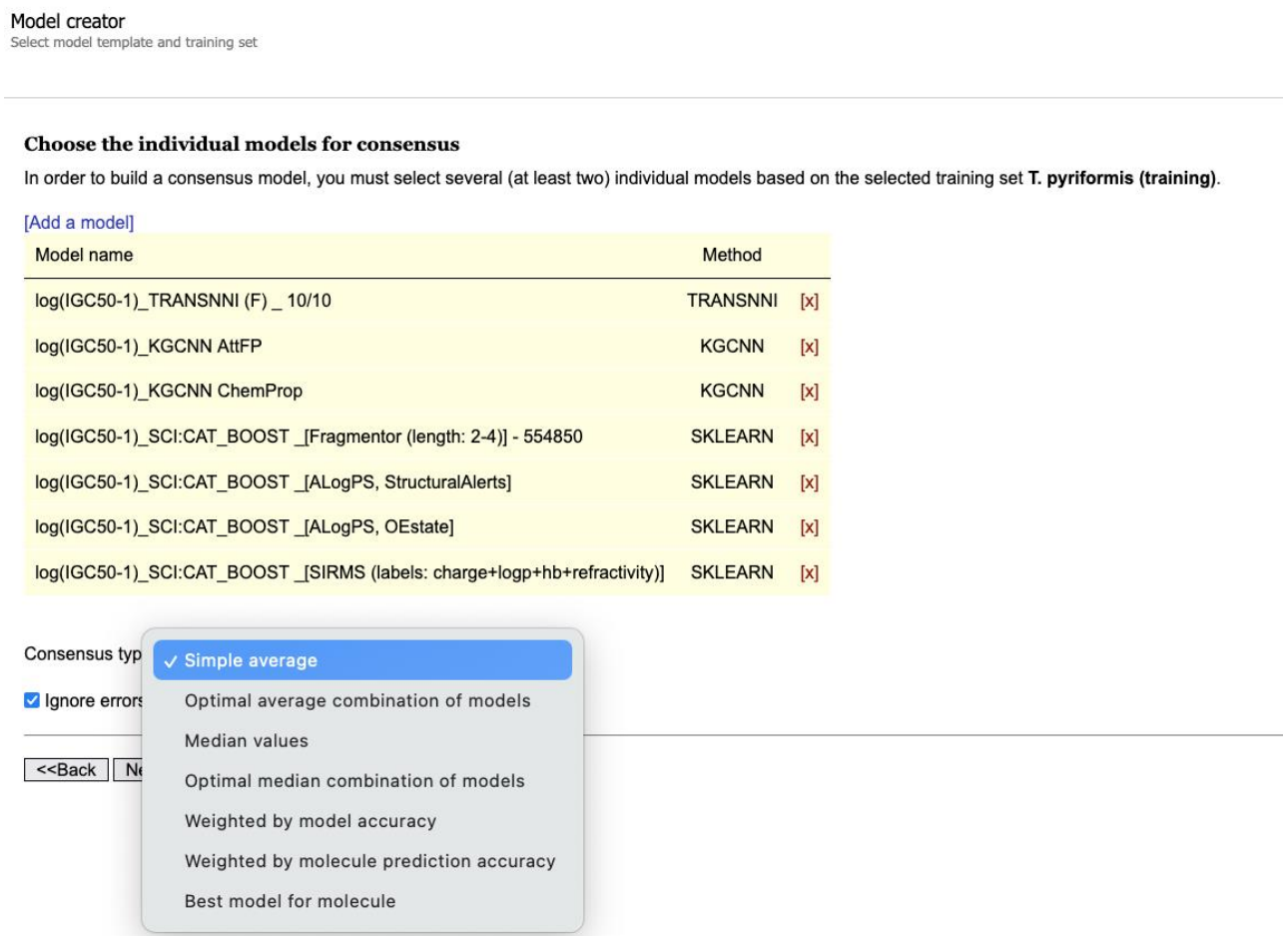


[Exclude duplicated records] [Exclude duplicated molecules]

Export this model | Create a copy of this model | View configuration XML | Export configuration XML | MI

PUBLISH THE MODEL | RECALCULATE MODEL AND STATISTICS | APPLY THE MODEL TO NEW COMPOUNDS

Consensus model development



Consensus model

Model profile

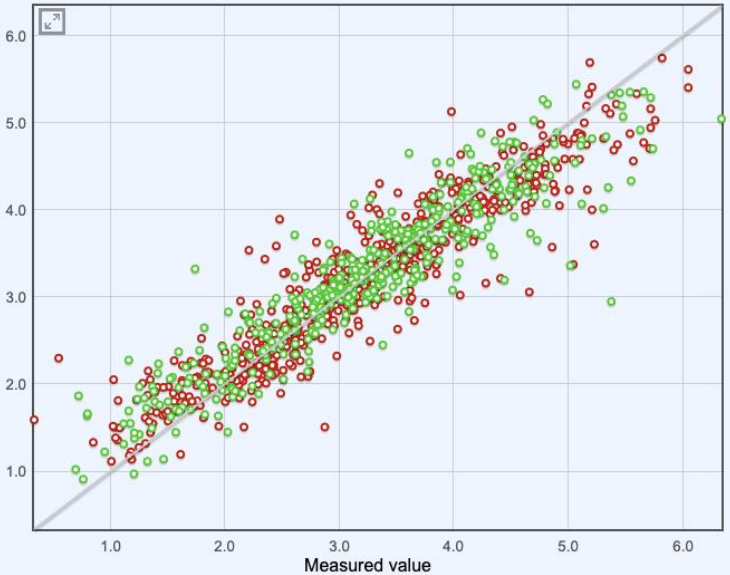
Statistical parameters, tables, charts - all the information related to the model.

Overview | Applicability domain

Model name: Consensus log(IGC50-1) [rename]
Temporal Public ID: 19562889 - use this link to share this temporal model (will be deleted after 3 months unless published)

Predicted property: **log(IGC50-1)** modeled in -log(mol/L)
Training method: Consensus

Data Set	#	R^2	q^2	RMSE	MAE
Training set: T. pyriformis (training)	644 records	0.87 ± 0.01	0.87 ± 0.01	0.38 ± 0.02	0.27 ± 0.01
Test set: T. pyriformis (test) [x]	449 records	0.86 ± 0.02	0.85 ± 0.02	0.4 ± 0.02	0.29 ± 0.01



[Exclude duplicated records] [Exclude duplicated molecules]

Models' overview: validation set

Metrics RMSE - Root Mean Square Error for Validation set Validation: All validation protocols

	ASNN (CHEMAXON)	DNN	Represent.	FSMLR	KNN	MLRA	PLS	LSSVMG	XGBOOST	RFR	SCI:CAT_BOOST
ALogPS, OEstate	+	0.51	+	+	+	+	+	+	+	+	0.43
ALogPS, StructuralAlerts	0.43	0.41	+	0.49	0.58	0.5	0.48	0.53	0.48	0.44	0.44
CDDD	+	0.48	+	+	+	+	+	+	+	+	0.53
CDK23 (cons,topol,geom,elect,hybr) 3D:rdkit3d	+	0.47	+	+	+	+	+	+	+	+	0.46
Dragon6 (2D blocks: 1 28)	+	0.66	+	+	+	+	+	+	+	+	0.7
Dragon7 (3D blocks: 1-30) 3D:rdkit3d	+	0.49	+	+	+	+	+	+	+	+	0.47
EPA (T.E.S.T.)	+	0.47	+	+	+	+	+	+	+	+	0.44
Fragmentor (length: 2-4)	running	0.5	+	0.48	0.62	0.53	0.44	0.6	0.48	0.5	0.46
GSFrag (F + L)	+	0.6	+	+	+	+	+	+	+	+	0.58
InductiveDescriptors 3D:rdkit3d	+	0.49	+	+	+	+	+	+	+	+	0.56
JPlogP	+	0.45	+	+	+	+	+	+	+	+	0.49
MNA	+	0.69	+	+	+	+	+	+	+	+	0.58
MOLD2	+	0.47	+	+	+	+	+	+	+	+	0.47
MORDRED (2D)	+	0.52	+	+	+	+	+	+	+	+	0.48
MORDRED (3D) 3D:rdkit3d	+	0.5	+	+	+	+	+	+	+	+	0.48
OEstate	0.46	0.43	+	0.49	0.6	0.49	0.48	0.5	0.52	0.5	0.46
OSMORDRED	+	0.49	+	+	+	+	+	+	+	+	0.47
QNPR (length:1 - 3)	+	0.53	+	+	+	+	+	+	+	+	0.49
RDKIT (2D blocks: 1-3 5 10-11 15-16)	+	0.5	+	+	+	+	+	+	+	+	0.45
RDKIT (3D blocks: 1-11 15-16) 3D:rdkit3d	+	0.53	+	+	+	+	+	+	+	+	0.48
RDKIT (ECFP4)	+	0.72	+	+	+	+	+	+	+	+	0.57
SIRMS (labels: charge+logp+hb+refractivity)	+	0.56	+	+	+	+	+	+	+	+	0.46
alvaDesc (2D blocks: 1-12 22-25 29 32-33)	+	0.5	+	+	+	+	+	+	+	+	0.48
alvaDesc (3D blocks: 1-33) 3D:rdkit3d	+	0.55	+	+	+	+	+	+	+	+	0.47
CNF2 (F) (3D) 10/10	+	+	0.45	+	+	+	+	+	+	+	+
DEEPCHEM (F) (3D) TEXTCNN 10/10	+	+	0.46	+	+	+	+	+	+	+	+
KGCNN AttFP	+	+	0.44	+	+	+	+	+	+	+	+
KGCNN ChemProp	+	+	0.48	+	+	+	+	+	+	+	+
TRANSNN (F) (3D) 10/10	+	+	0.5	+	+	+	+	+	+	+	+
TRANSNNI (F) 10/10	+	+	0.43	+	+	+	+	+	+	+	+

	Consensus:AVERAGE
Consensus log(IGC50-1)	0.4

Each descriptor/method sees only part of a molecule

Blind monks examining an elephant, an ukiyo-e print by Hanabusa Itchō (1652–1724).
https://en.wikipedia.org/wiki/Blind_men_and_an_elephant

OCHEM modeling

- Comprehensive modeling
- Multitask learning (up to 100 properties)
- Feature net (“model in model”)
- Consensus models
- GPU + CPU modern methods (~20)
- Supports models
  - >1,000,000 compounds
  - >200,000,000,000 descriptors*
  - >1,000 servers
  - up to 1GB in size (Java limit)
- Model private/publishing
- Export, import, web/REST services
- Conditions, external descriptors
- ToxAlerts screening

Predicted property: LLNA skin sensitization
Training set: TRAINING-SARpy-SKIN-SENS-giugno20 OK.xlsx

Metrics AUC for Training set Validation: Cross-Validation (84 models)

	LSSVMG	ASNN	PLS	KNN
ALogPS, OEstate	0.74	0.68	0.61	0.64
CDDD	0.8	0.74	0.75	0.71
CDK2 (cons,topol,geom,elec,hybrid) 3D:corina	0.75	0.71	0.56	0.71
ChemaxonDescriptors (pH 0 - 14:1) 3D:corina	0.76	0.7	0.59	0.68
Dragon6 (2D blocks: 1 28)	0.64	0.66	0.59	0.65
Dragon6 (3D blocks: 1-29) 3D:corina	0.76	0.72	0.57	0.65
Fragmentor (length:2 - 4)	0.72	0.7	0.59	0.63
GSFrag (F + L)	0.69	0.69	0.61	0.61
InductiveDescriptors 3D:corina	0.69	0.71	0.57	0.67
JPlogP	0.73	0.74	0.59	0.67
MAP4	0.71	0.65	0.59	0.67
MORDRED (All) 3D:corina	0.77	0.73	0.57	0.68
Mera, Mersy 3D:corina	0.73	0.69	0.55	0.67
OEstate	0.74	0.67	0.63	0.68
PyDescriptor 3D:corina	0.71	0.71	0.7	0.67
QNPR (length:1 - 3)	0.68	0.62	0.58	0.58
RDKIT (3D blocks: 1-11 15-16) 3D:corina	0.77	0.72	0.56	0.65
SIRMS (labels:charge+logp+hb+refractivity)	0.76	0.73	0.59	0.67
Spectrophores (accuracy=20) 3D:corina	0.68	0.6	0.52	0.6
StructuralAlerts	0.67	0.64	0.58	0.51
alvaDesc (3D blocks: (only) 1-30) 3D:corina	0.75	0.71	0.57	0.68

* Sparse format, DOI:10.1186/s13321-016-0113-y

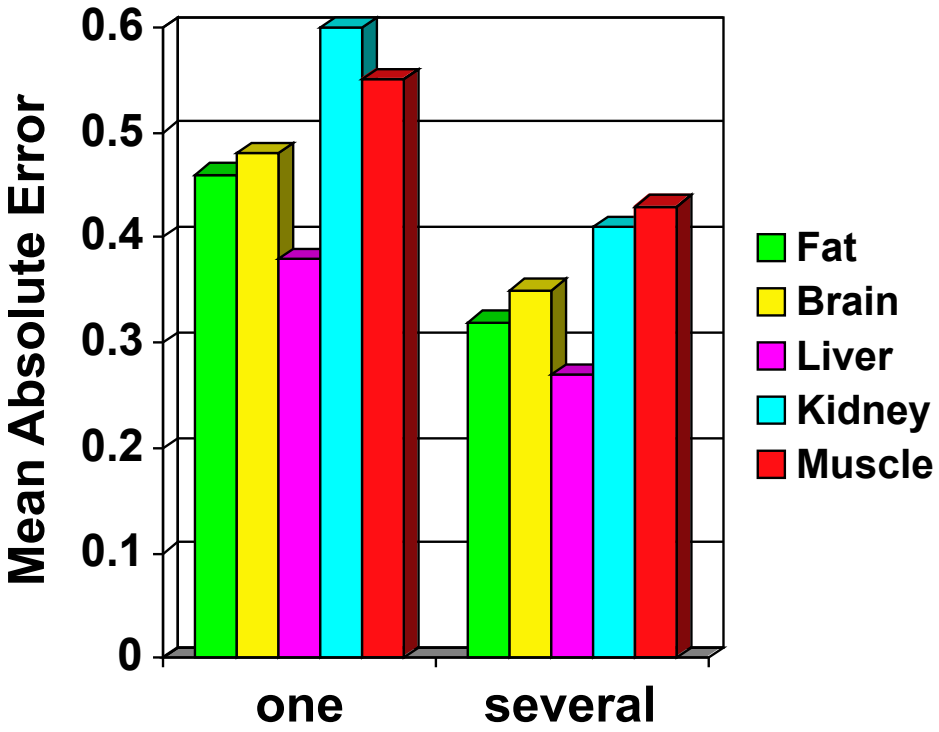
Multi-task learning

Problem:

• prediction of tissue-air partition coefficients
• small datasets 30-100 molecules (human & rat data)

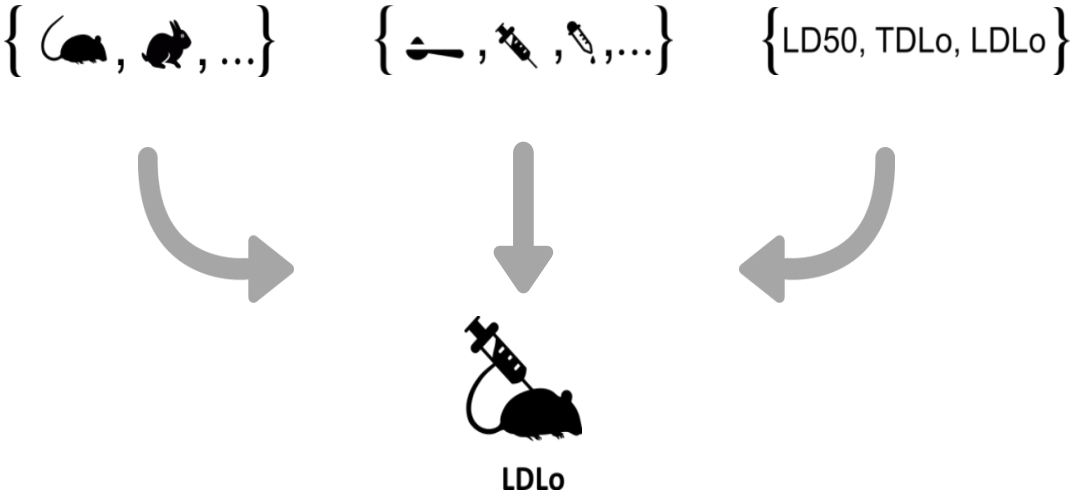
Results:

simultaneous prediction of several properties increased the accuracy of models



Varnek, A. et al *J. Chem. Inf. Model.* 2009, 49, 133-44.

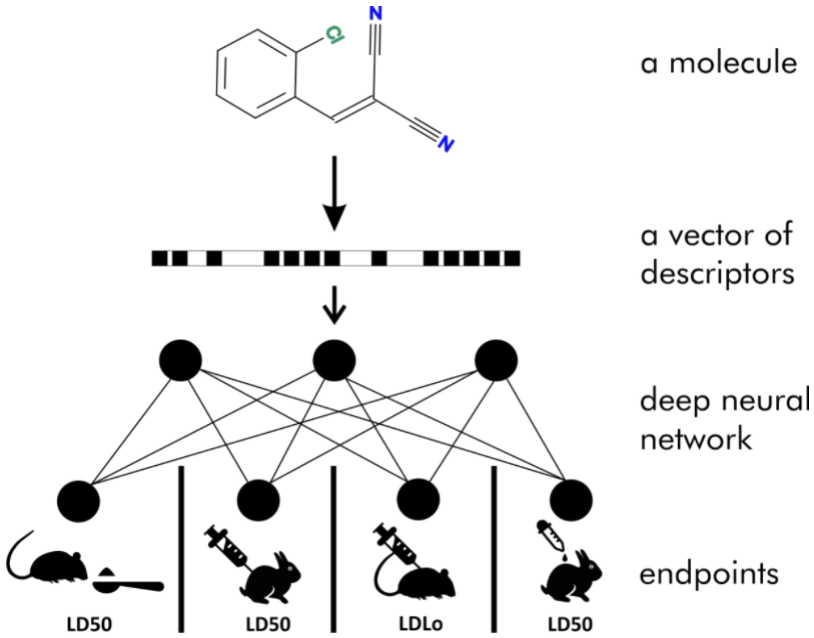
Analysis of toxicity of chemical compounds



129 142 toxicity measurements from RTECS*

87 064 unique molecular structures

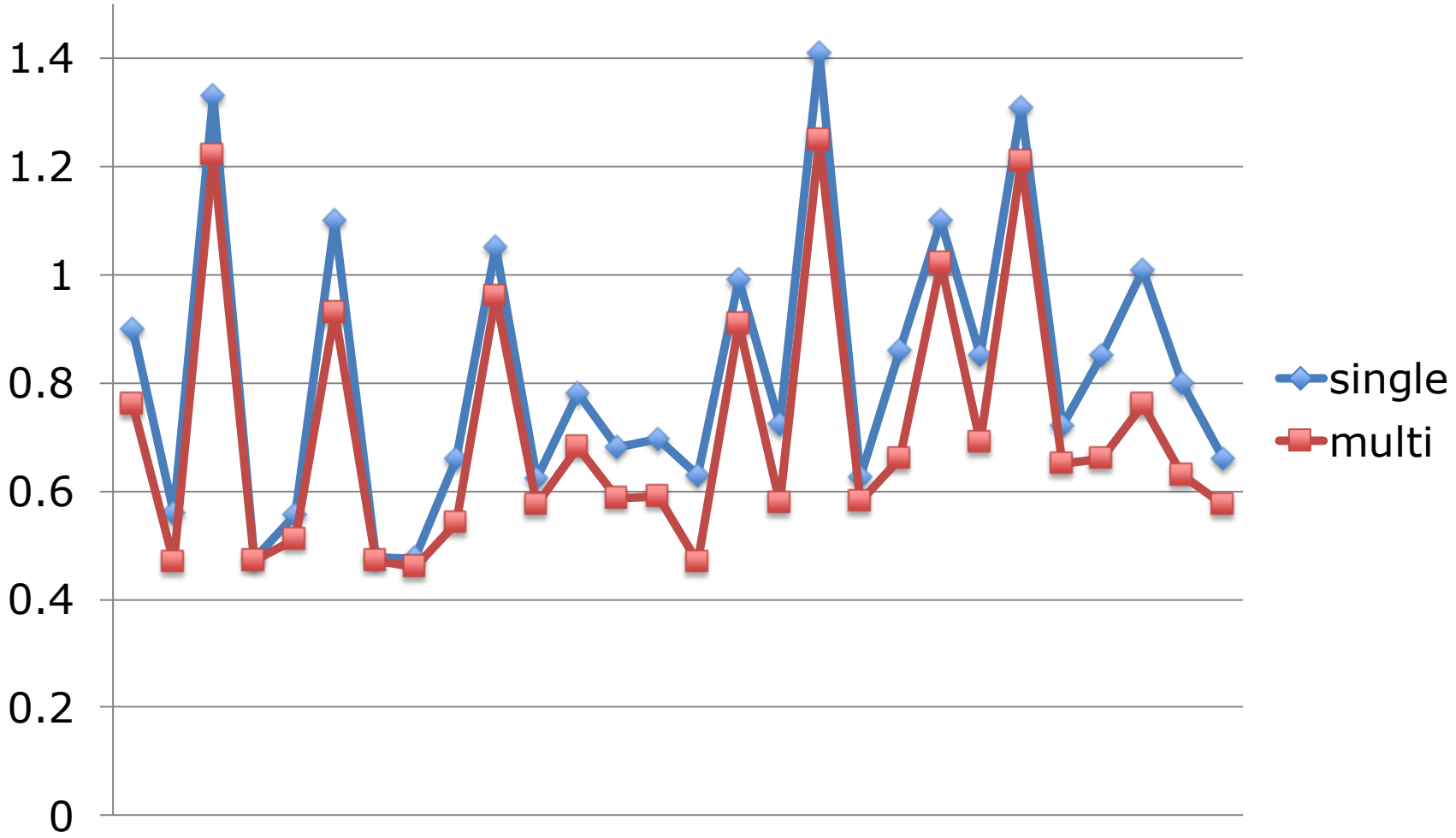
29 toxicity endpoints



*RTECS: Registry of Toxic Effects of Chemical Substances

Sosnin, S. et al. *J. Chem. Inf. Model.*, **2018**, 59:1062-1072.

RMSE for different toxicities using CDK descriptors and DNN



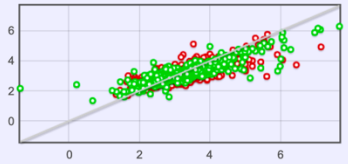
Sosnin, S.; Karlov, D.; Tetko, I.V.; Fedorov, M.V. A comparative study of prediction of multi-target toxicity for a broad chemical space. *J Chem Inf Model.* ***2018,*** **59**, 1062-1072.

Comprehensive model view

Model name: Consensus all[apply to new compounds]
Training method: Consensus

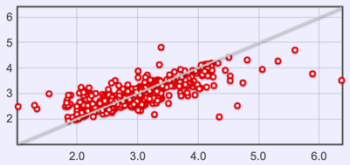
Property: mouse_intraperitoneal_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(36295)	0.65	0.41	0.26
uniques in RTECS(5189)	0.77	0.38	0.25



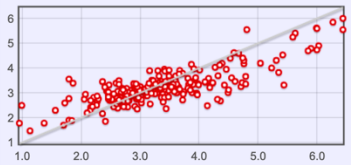
Property: mammal (species unspecified)_intraperitoneal_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(545)	0.61	0.42	0.26
uniques in RTECS(0)	0.00	0.00	0.00



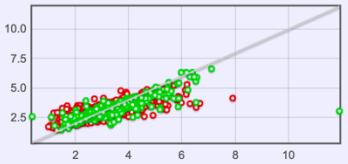
Property: guinea pig_intraperitoneal_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(248)	0.66	0.60	0.44
uniques in RTECS(0)	0.00	0.00	0.00



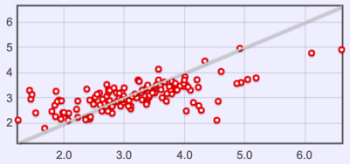
Property: rat_intraperitoneal_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(5021)	0.63	0.53	0.36
uniques in RTECS(933)	0.72	0.47	0.25



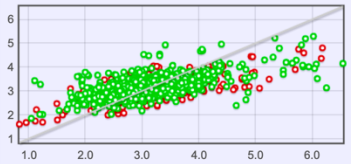
Property: rabbit_intraperitoneal_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(131)	0.46	0.69	0.50
uniques in RTECS(0)	0.00	0.00	0.00



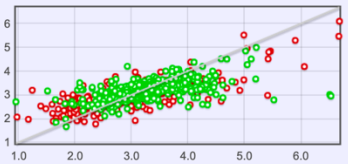
Property: mouse_intraperitoneal_LDLo measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(266)	0.54	0.62	0.48
uniques in RTECS(2678)	0.44	0.52	0.38



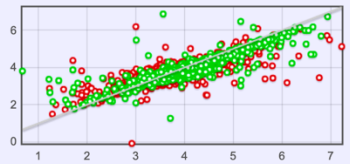
Property: rat_intraperitoneal_LDLo measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(318)	0.61	0.55	0.40
uniques in RTECS(757)	0.35	0.46	0.30



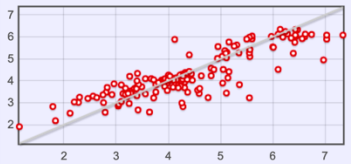
Property: mouse_intravenous_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(16978)	0.67	0.42	0.28
uniques in RTECS(4151)	0.82	0.35	0.22



Property: guinea pig_intravenous_LD50 measured in -log(M) (Details..)

Dataset	R^2	RMSE	MAE
data_upload_new.csv(153)	0.75	0.64	0.47
uniques in RTECS(0)	0.00	0.00	0.00



Comparison of different models to predict toxicity (RMSE)

single multi single

Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (63 models)

	DNN	DNN(2)	XGBOOST
CDK2 (constitutional, topological, geometrical, electronic, ...	0.9 0.56 1.33 0.474 0.56 1.1 0.478 0.477 0.66 1.05 0.623 0.78 0.68 0.7 0.63 0.99 0.724 1.41 0.63 0.86 1.1 0.85 1.31 0.72 0.85 1.01 0.8 0.66 1.27 (0.834)	0.76 0.47 1.22 0.472 0.51 0.93 0.471 0.459 0.54 0.96 0.576 0.68 0.59 0.591 0.47 0.91 0.577 1.25 0.581 0.66 1.02 0.69 1.21 0.65 0.66 0.76 0.63 0.58 1.14 (0.725)	0.8 0.47 1.29 0.454 0.5 1.02 0.466 0.439 0.56 1.04 0.584 0.75 0.6 0.65 0.59 0.95 0.66 1.33 0.585 0.75 1.08 0.764 1.3 0.67 0.81 0.88 0.76 0.63 1.2 (0.779)
Dragon6 (blocks: 1-29)	0.89 0.58 1.3 0.458 0.56 1.06 0.481 0.472 0.6 1.06 0.63 0.74 0.66 0.686 0.63 0.97 0.69 1.32 0.622 0.82 1.09 0.83 1.33 0.76 0.83 0.98 0.8 0.7 1.24 (0.82)	0.78 0.44 1.31 0.445 0.474 0.96 0.461 0.446 0.52 1 0.555 0.68 0.55 0.581 0.47 0.95 0.57 1.31 0.574 0.65 1.08 0.68 1.2 0.68 0.67 0.74 0.64 0.59 1.22 (0.732)	0.8 0.49 1.3 0.454 0.523 1.01 0.47 0.439 0.59 1.02 0.588 0.73 0.61 0.66 0.602 0.94 0.67 1.33 0.585 0.76 1.09 0.77 1.38 0.68 0.82 0.88 0.74 0.63 1.24 (0.786)
ALogPS, OEstate	0.91 0.61 1.32 0.461 0.54 1.1 0.478 0.469 0.6 1.1 0.617 0.75 0.7 0.652 0.64 1 0.69 1.36 0.617 0.84 1.11 0.87 1.43 0.76 0.85 0.95 0.8 0.71 1.2 (0.832)	0.79 0.44 1.23 0.447 0.49 0.94 0.467 0.444 0.53 0.99 0.554 0.66 0.55 0.59 0.49 0.9 0.58 1.21 0.571 0.65 1.05 0.69 1.22 0.65 0.7 0.74 0.64 0.6 1.17 (0.724)	0.84 0.5 1.42 0.456 0.519 1 0.469 0.44 0.56 1.03 0.58 0.73 0.581 0.65 0.61 0.95 0.64 1.34 0.59 0.77 1.11 0.79 1.33 0.69 0.8 0.81 0.75 0.63 1.21 (0.786)
Fragmentor (Length 2 - 4)	0.96 0.61 1.43 0.463 0.542 1.14 0.491 0.484 0.62 1.1 0.647 0.81 0.71 0.71 0.64 1.04 0.74 1.38 0.643 0.79 1.14 0.86 1.33 0.82 0.86 0.94 0.84 0.66 1.22 (0.849)	0.73 0.45 1.25 0.44 0.48 0.95 0.465 0.448 0.502 0.99 0.554 0.65 0.55 0.56 0.46 0.92 0.575 1.28 0.564 0.63 1.07 0.69 1.24 0.7 0.66 0.73 0.63 0.62 1.2 (0.724)	0.78 0.45 1.38 0.447 0.52 1.07 0.476 0.436 0.58 1.09 0.592 0.75 0.61 0.67 0.59 0.94 0.67 1.3 0.589 0.77 1.14 0.79 1.43 0.69 0.83 0.82 0.77 0.64 1.29 (0.797)

Sosnin, S. et al. A comparative study of prediction of multi-target toxicity for a broad chemical space. *J Chem Inf Model.* 2019, **59**, 1062-1072.

Incorrect multitask validation

Model validation

Validation method: N-Fold cross-validation

Number of folds: 5

☐ Stratified cross-validation (classification only)

☐ Treat each record as a new molecule

☐ (Experimenal) Use scaffold-based split

Multiple models overview

Predicted property: Cblood/Cair(Human)
Training set: blood_tissue
Duplicate models: start

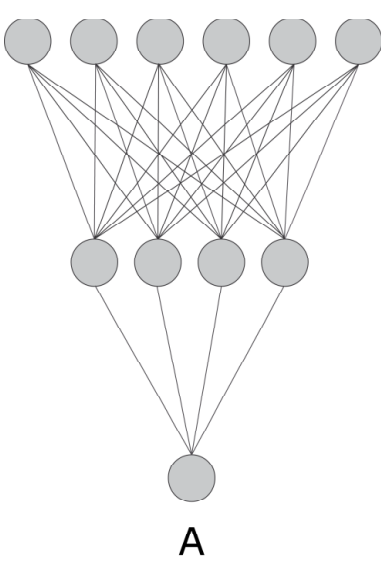
Metrics RMSE - Root Mean Square Error for Training set Validation: Cross-Validation (3 models)

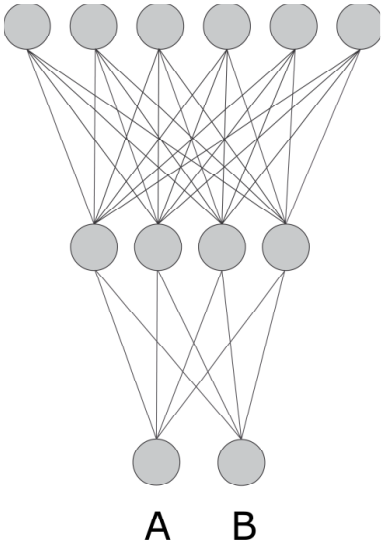
	ASNN	ASNN (STL)	ASNN (record)
Fragmentor (length: 2-4)	0.52 0.4 0.25 0.28 0.32 0.3 0.37 0.44 0.45 0.41 0.38 1.4 (0.46)	0.59 0.55 0.35 0.64 0.48 0.44 0.42 0.61 0.51 0.51 0.4 1.3 (0.5667)	0.47 0.3 0.15 0.16 0.24 0.2 0.3 0.27 0.3 0.3 0.39 1.3 (0.365)

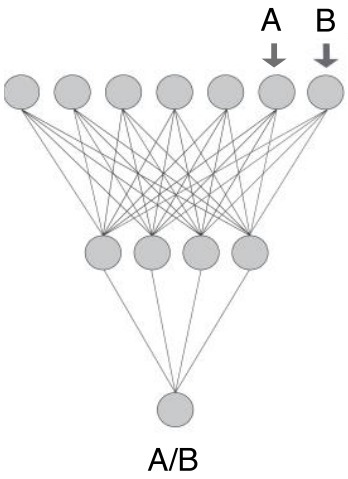
Predicates ("<", ">") and/or optimal classification thresholds are NOT used for statistics (click to change)

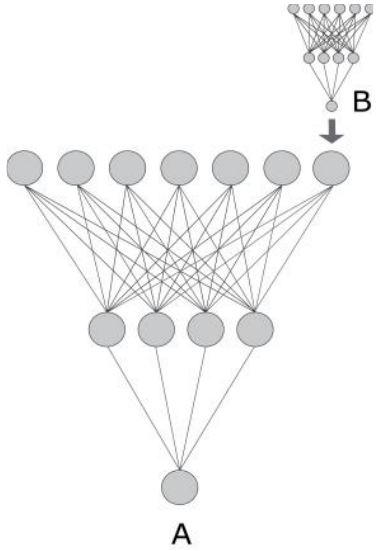
Refresh

Multi-task learning



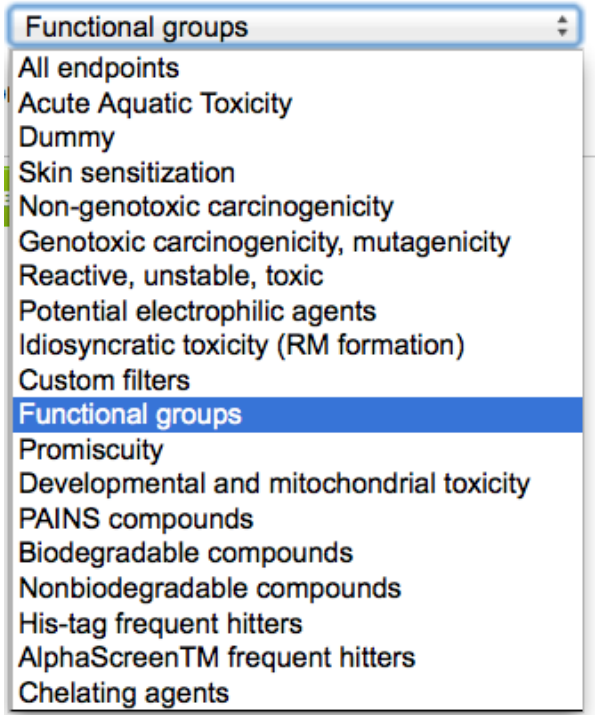


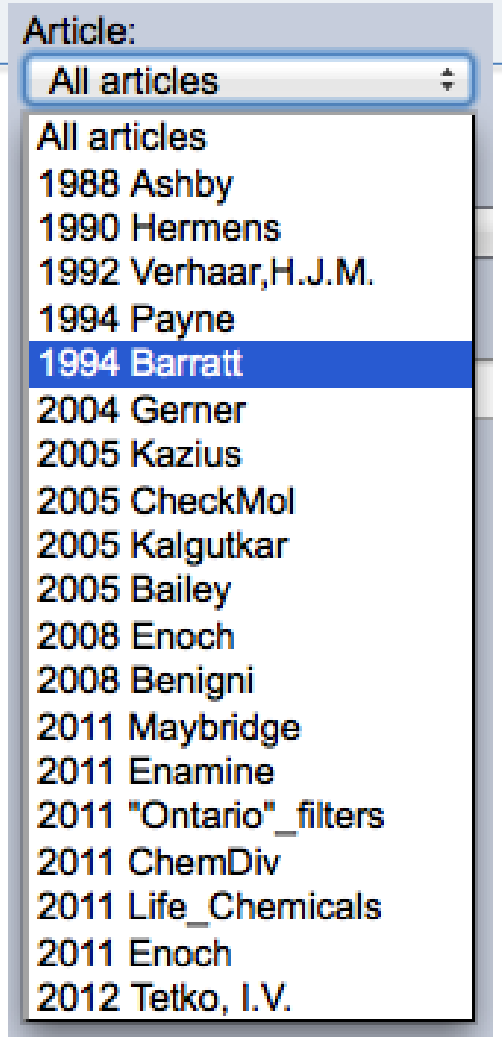




ToxAlerts

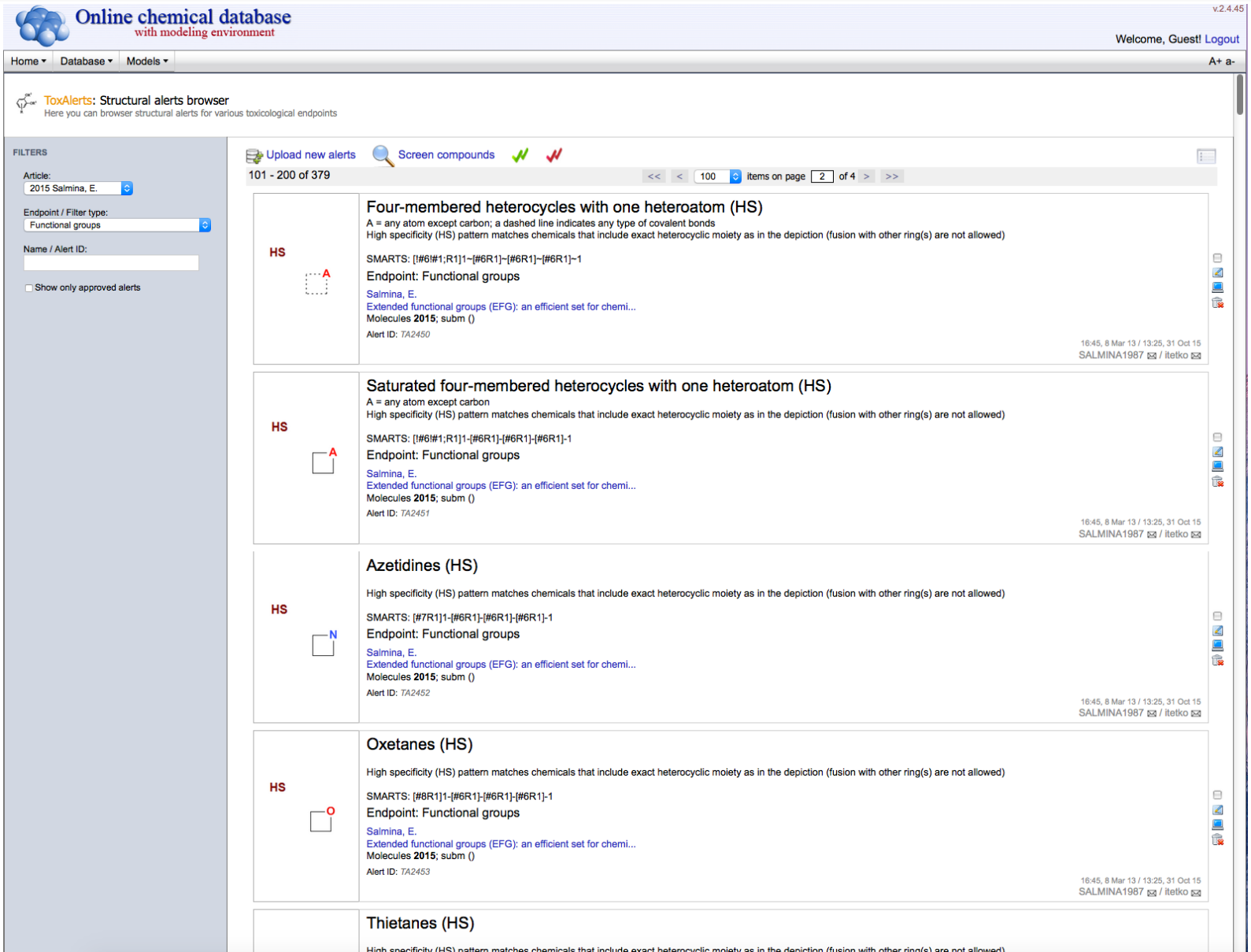
- Screening of compounds against published toxicity alerts, groups, frequent hitters
- Filter alerts by endpoints or publications
- Create or upload custom SMARTS rules



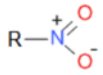
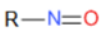
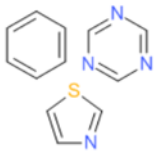


Sushko et al, JCIM, 2012, 52(8):2310-6. Salmina et al, Molecules, 2015, 21.

Functional groups



Overrepresented functional groups for AMES

	Active	Inactive		
Descriptor	**In set 1 (3514 unique molecules)**	**In set 2 (3023 unique molecules)**	**Enrichment factor**	**p-Value**
	808 (23.0%)	167 (5.5%)	4.2	1.545E-94
Pnictogens Group 15: the nitrogen family **N P As Sb Bi**	2498 (71.1%)	1714 (56.7%)	1.3	5.687E-34
	219 (6.2%)	28 (0.9%)	6.7	2.796E-33
	2546 (72.5%)	1782 (58.9%)	1.2	7.944E-31
	2770 (78.8%)	2004 (66.3%)	1.2	3.461E-30

Using SetCompare functionality and selecting EFG as descriptors

Classification model for AMES test

Mopac2016 descriptors

Y = 0.5378 - 0.3411*MullikenElectronegativity - 0.3277*LumoEnergy + 0.2389*IonisationPotential + 0.1178*FinalHeat + 0.05051*DipolPointCharge

GSFRAG

Y = 0.5372 + 0.1612*c10 + 0.1309*p1-1N - 0.1134*p2B + 0.05943*c3 + 0.05349*c9

E-state descriptors

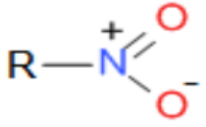
Y = 0.5375 + 0.09956*PSA + 0.08731*aCNOS - 0.08703*DONORS - 0.06814*SsCH3 - 0.04474*SssO

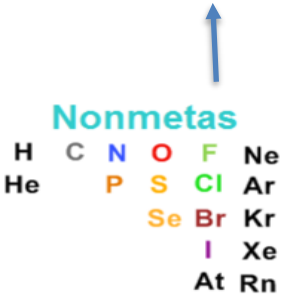
Dragon descriptors

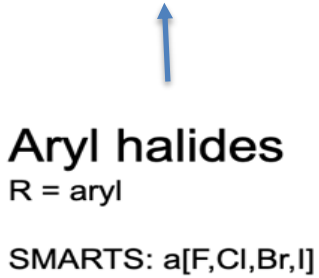
Y = 0.5375 - 0.1173*GATS1m + 0.0954*MATS1e - 0.06558*SpMax_AEA(dm) + 0.05933*J_D/Dt + 0.05496*nR03

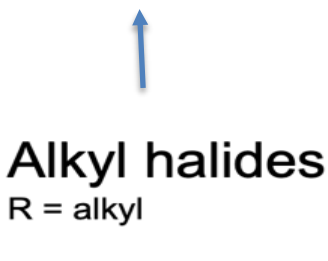
Functional groups

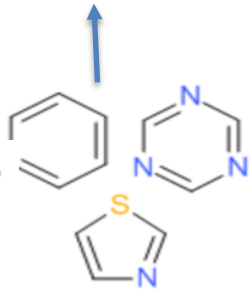
Y = 0.4733 + 0.191*Alert146 - 0.00411*Alert238- 0.1024*Alert213 + 0.1912*Alert214+ 0.0199*Alert196



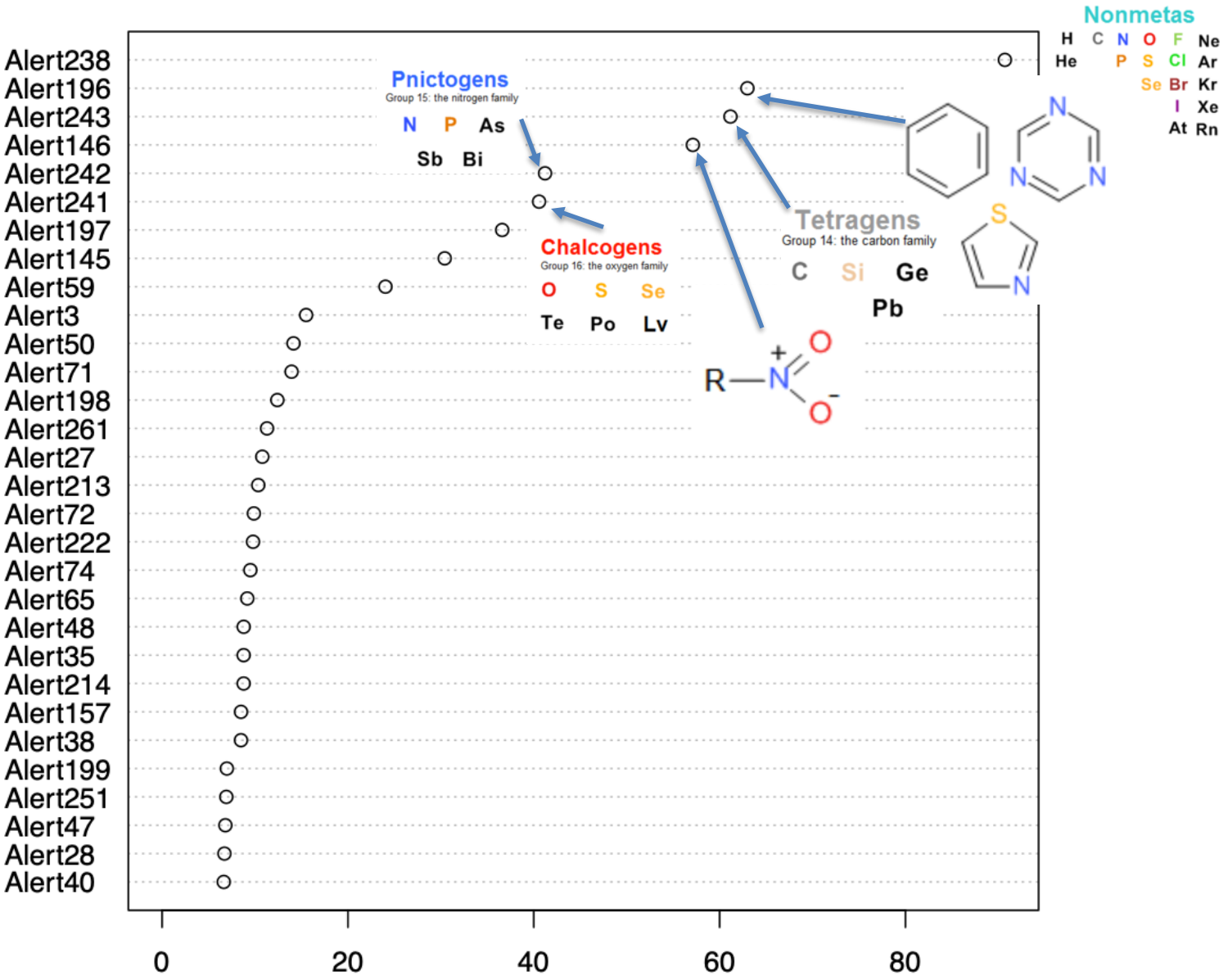








Importance of ToxAlerts in Random Forest model



Tox24 Challenge

EPA submitted an article in February with results of screening of TTR-intefering compounds

March-April: negotiation with EPA, ChemResTox, ICANN2024, AIDD to organize the challenge

May 17th – data are publicly available

- 1012 training set
- 200 LeaderBoard set
- 300 Blind Test set

August 15th

- LeaderBoard set is available

September 1st

- Results announced

ICANN24

33rd International Conference on Artificial Neural Networks

Home **Conference** Registration Contributors Organisation T

Tox24 Challenge

The **Tox24** challenge is designed to assess the progress in computational methods for predicting in vitro activity of compounds. All ML experts are strongly invited to participate in it and compete for a prize of **1000€**, to be awarded for the winning model.

Eytcheson, S. A.; Tetko, I. V. Which Modern AI Methods Provide Accurate Predictions of Toxicological End Points? Analysis of Tox24 Challenge Results. *Chem. Res. Toxicol*. **2025**, 38 (9), 1443–1451. https://doi.org/10.1021/acs.chemrestox.5c002

Tox24 Challenge results

Tox24 final ranking based on the blind set - congratulations to the winning team Amidoff!
In case of equal performances the earlier entry was used. Models with lower RMSE (Root Mean Squared Error) are better.
You can access the winning model here

rank	User	submission id	*** Blind test set RMSE ***	Leaderboard set RMSE	Submission time (GMT-12)
1	Amidoff	1148	20.5	7.8	25-08-2024 06:13:02
2	tcirino	1098	20.7	4.1	21-08-2024 08:53:04
3	znavoyan	1309	20.7	5.7	30-08-2024 07:16:19
4	uesawa	1149	20.8	21.2	25-08-2024 14:03:09
5	YingkaiZhangLab	1388	20.8	20.7	31-08-2024 06:49:33
6	AntonijaBoss	1400	21.2	20.6	31-08-2024 09:07:16
7	SankalpJain	1284	21.3	5.1	30-08-2024 02:46:16
8	alx.dga	1097	21.4	0.0	21-08-2024 08:45:46
9	luispintoc	1209	21.4	15.0	28-08-2024 06:00:04
10	GAT_Wang	1253	21.4	6.0	29-08-2024 15:26:28
11	vchupakhin	1404	21.4	3.2	31-08-2024 13:34:03

Follow up study by the EPA (JCIM)

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim Article

Combined *In Vitro* and *In Silico* Workflow to Deliver Robust, Transparent, and Contextually Rigorous Models of Bioactivity

Nathaniel Charest,* Gabriel Sinclair, Stephanie A. Eytcheson, Daniel T. Chang, Todd M. Martin, Charles N. Lowe, Katie Paul Friedman, and Antony J. Williams

Cite This: *J. Chem. Inf. Model.* 2025, 65, 4426–4441 Read Online

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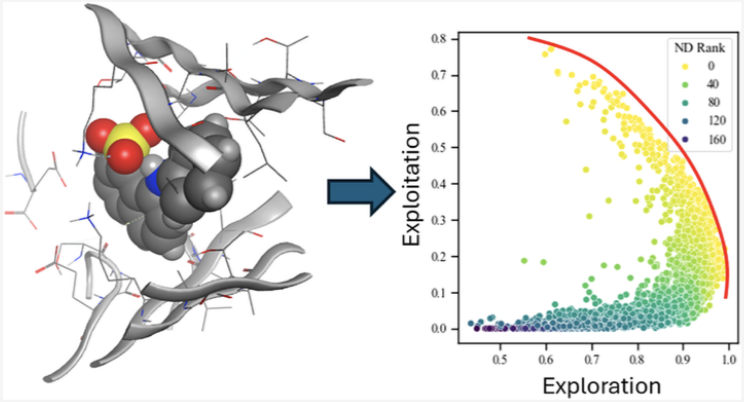
ABSTRACT: New approach methodologies (NAMs) are an increasing priority in the field of toxicology to fill data gaps and reduce time and resources in chemical safety assessment. We describe an NAMs workflow that integrates an *in vitro* high-throughput bioassay with an *in silico* computational model. In defining this workflow, we propose, as a crucial step of *in silico* development, the identification of explicit "purpose contexts": *a priori* definitions of the scope and intent of an *in silico* solution, which provide natural targets for the mechanistic interpretation, validation, and output design of the model. By inspecting data from an *in vitro* assay measuring the displacement of fluorescent probe 8-anilino-1-naphthalenesulfonic acid (ANSA) from the serum transport protein transthyretin (TTR) as a proxy for potential



Descriptors from JCIM article

FEATURE	DESCRIPTOR MEANING
CrippenLogP	A group contribution model of predicted water-octanol partition coefficient
ATSC3c	The autocorrelations of lag 3 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.
ATSC5c	The autocorrelations of lag 5 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.
C1SP3	Number of SP3 hybridized carbons.
ETA_BetaP_s	A measure of electrons in resonance.
naAromAtom	Number of aromatic atoms in the molecular graph
ZMIC5	A measure of neighborhood in the molecular graph symmetry. ZMIC(n) where n is the radius of the neighborhood unit.
ATSC4m	The autocorrelations of lag 4 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
ZMIC1	A measure of neighborhood in the molecular graph symmetry. ZMIC(n) where n is the radius of the neighborhood unit.
C1SP2	Number of SP2 hybridized carbons.
hmax	Maximum electronic state of the molecule.
ATSC2m	The autocorrelations of lag 2 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
hmin	Minimum electronic state of the molecule.
ATSC0m	The autocorrelations of lag 0 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
ZMIC2	A measure of neighborhood in the molecular graph symmetry. ZMIC(n) where n is the radius of the neighborhood unit.
ATSC5m	The autocorrelations of lag 5 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
ATSC4c	The autocorrelations of lag 4 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.
VE1_DzZ	The sum of coefficients from the first eigenvector of the Barysz matrix. Very abstract, but a summary descriptor for capturing heteroatomic topological similarity. Useful for global molecular s
nHBAcc	Number of hydrogen bond acceptors.
ETA_dAlpha_A	Measure of number of heteroatoms
ZMIC3	A measure of neighborhood in the molecular graph symmetry. ZMIC(n) where n is the radius of the neighborhood unit.
ETA_Beta_ns_d	A set of descriptors capturing, in order, a measure of non-hydrogen heteroatoms; a measure of hydrogen bonding propensity; and electrons within a resonance structure. Specifically, the nun
ATSC1m	The autocorrelations of lag 1 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
ATSC2c	The autocorrelations of lag 2 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.
ATSC3m	The autocorrelations of lag 3 within the molecular graph weighted by mass. Useful for capturing local structure motifs or patterns that encode bioactivity.
maxdssC	An electrotopological index capturing carbons with a double bond and two single bonds. Included due to senstivity to aromatized carbons with substituent bonds.
ATSC0c	The autocorrelations of lag 0 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.
ETA_Shape_Y	A measure of hydrogen bonding propensity of the molecule.
ZMIC4	A measure of neighborhood in the molecular graph symmetry. ZMIC(n) where n is the radius of the neighborhood unit.
nHBDon	Number of hydrogen bond donors.
ATSC1c	The autocorrelations of lag 1 within the molecular graph weighted by charge. Useful for capturing local structure motifs or patterns that encode bioactivity.

"Data matters!"

#	Training set size	RMSE, 5CV training set	RMSE, test set	Sensitivity, %	Balance accuracy,[1] %	Model
0	639	-	-	77	80	Original study by EPA
I	639	22.0±0.6	21 ± 1	88	87	https://ochem.eu/model/1266
II	1298	22.7±0.6	19 ± 1	91	89	https://ochem.eu/model/1212
III	639	23.5±0.6	21 ± 1	81	83	https://ochem.eu/model/1268
IV	1298	24.3±0.6	20 ± 1	84	85	https://ochem.eu/model/1267

I-II developed using the winning model protocol

III & IV are developed using logP/S + Extended Functional Groups*

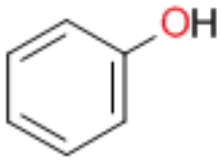
Salmina, E. S.; Haider, N.; Tetko, I. V. Extended Functional Groups (EFG): An Efficient Set for Chemical Characterization and Structure-Activity Relationship Studies of Chemical Compounds. Molecules. 2015, 21 (1), E1. https://doi.org/10.3390/molecules21010001.

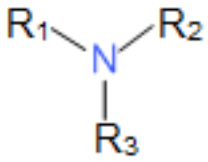
Model built using functional groups

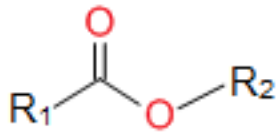
MLRA model

$$Y = 27.47 + 12.72*ALogPS\_logP + 16.58*TA1139 + 1.051*TA1301 - 1.289*TA1340 + 5.556*TA1343 + 9.262*TA1169 - 6.594*TA1315 + 9.814*TA1152 - 5.707*TA1178$$

TA1139 – Phenols; TA1301 - Aromatic compounds;
TA1340 – Nonmetals; TA1343 – Chalcogens;
TA1169 - Aryl chlorides; TA1315 - Aryl halides;
TA1152 – Amines; TA1178 - Carboxylic acid esters;



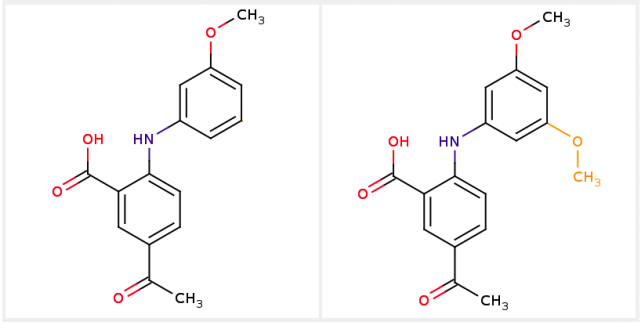




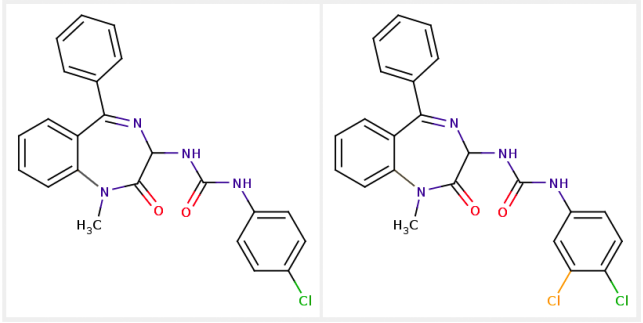
MMP definition

A molecular matched pair (MMP) is a pair of molecules that have only a (minor) single-point difference.
The typical way is to define a minor difference as a changed molecular fragment with less than 10 atoms.

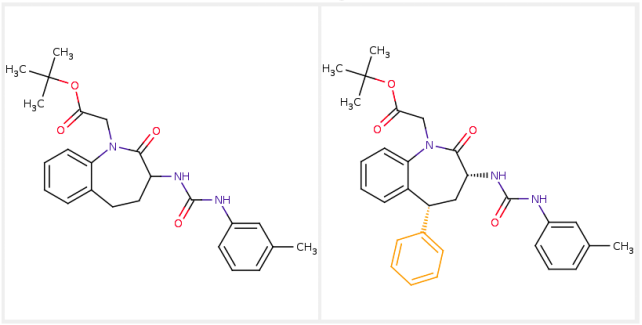
Pair 1



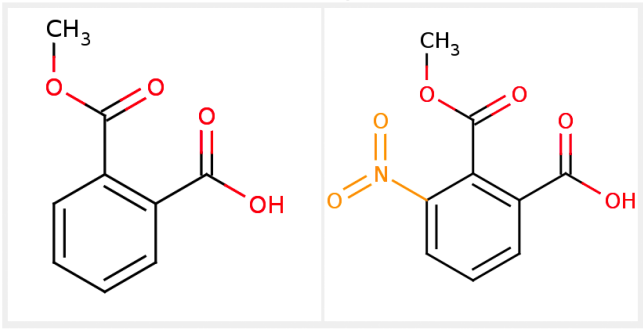
Pair 2



Pair 3



Pair 4



View historical facts

- Term was first introduced in 2005 by Kenny and Sadowski
- Popularized by works of A. Leach, J. Bajorath, etc.
- Commercially distributed by MedChemica
- Publicly available in KNIME, OCHEM, etc.
- 2013: Roche, AZ and MedChemica formed consortium with a goal

“extracts the pre-competitive knowledge of how to design drugs, and combines these into a large database, which all the members of the consortium use”.

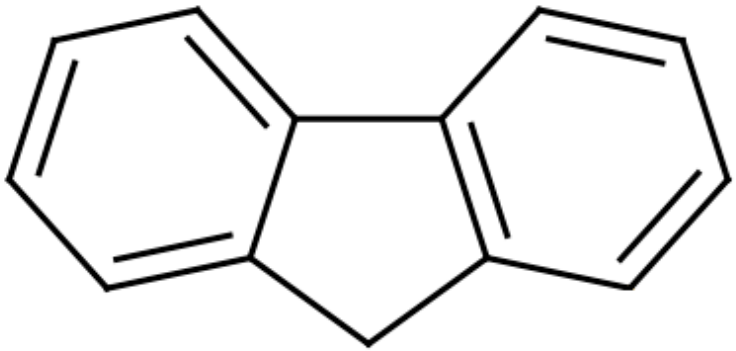
Why MMPs?

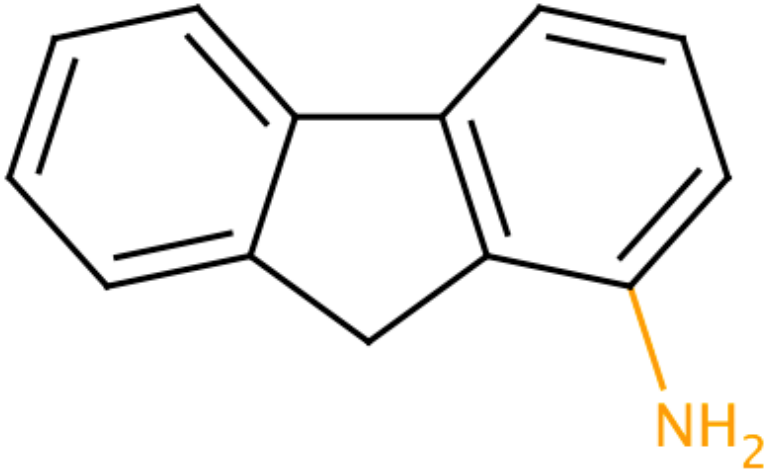
Keyword: **interpretation**

Small localized changes allow for interpreting activity

- Identification of interpretable activity cliffs
- Identification of “significant” transformations
- Interpretation of models

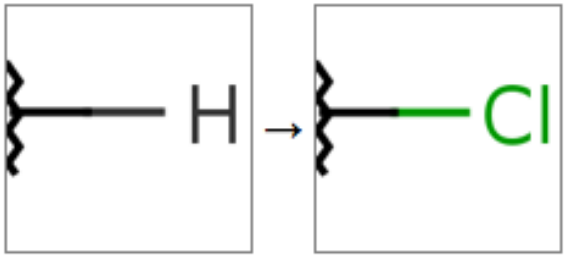
MMP example





Melting Point	= 112.0 – 116.0 (in °C)	= 125.5 (in °C)
AMES	= inactive	= active
logPow	= 4.18 (in Log unit)	= 3.18 (in Log unit)

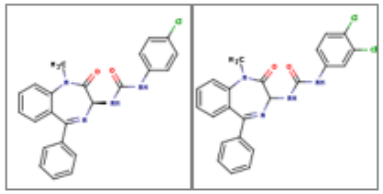
MMPs and transformations

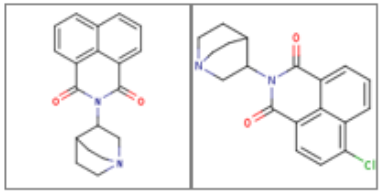


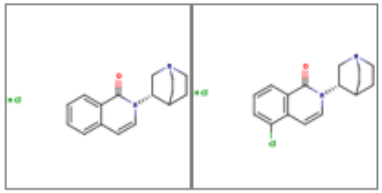
Transformation ID: TR3651887
SMIRKS: *[H] -> *Cl


M1000289022 M1000288950

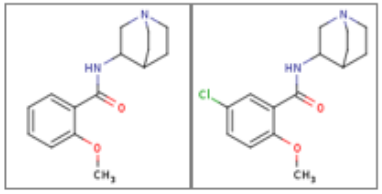

M1000289025 M1000288950

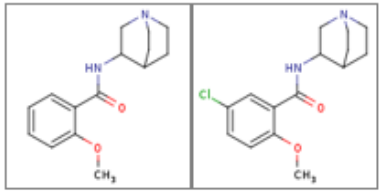

M1000289110 M1000288950

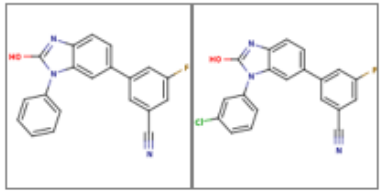

M1000303314 M1000303365


M1000303309 M1000303347

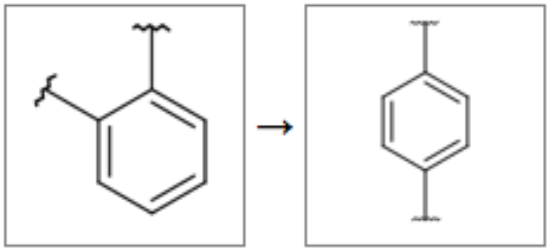

M1000289025 M1000288930


M1000303332 M1000303429

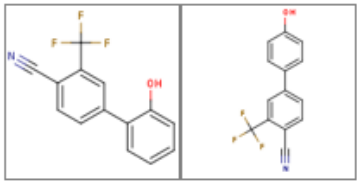

M1000303332 M1000303429

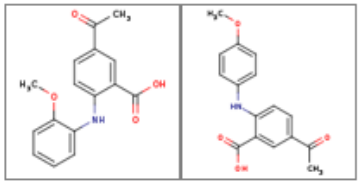

M1000050303 M1000050306

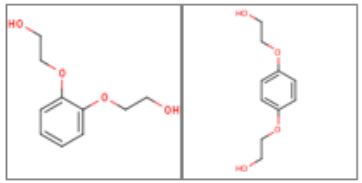
MMPs and transformations

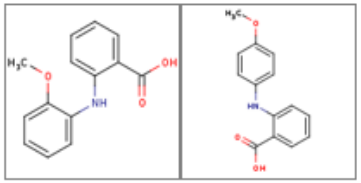


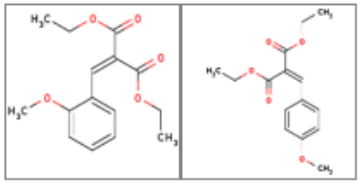
Transformation ID: TR3651270
SMIRKS: *C1=CC=CC=C1* -> *C1=CC=C(*)C=C1

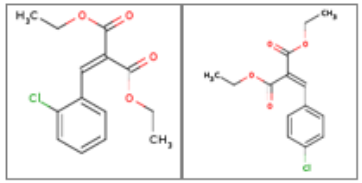

M1000050341 M1000050340

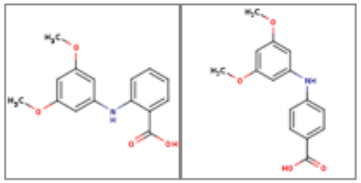

M1002111542 M1002111562

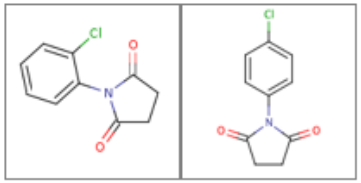

M108286 M65324

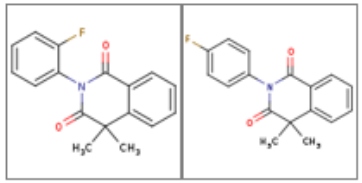

M1002111554 M1001278883


M31447 M31448


M31445 M31477


M1002111513 M1002111550


M31913 M31550

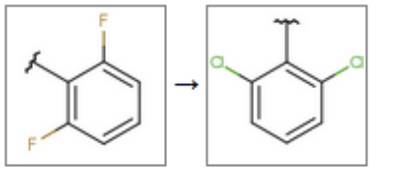

M1000050431 M1000050429

MMPs for quantitative activity data

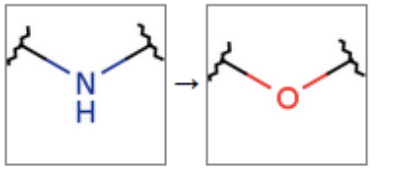
The info is based on dataset **ic50_RT HIV** for property **IC50 HIV**
Minimal pair similarity: 50

MMP transformations: minimum 4 pairs, p-value 0.05 , max.

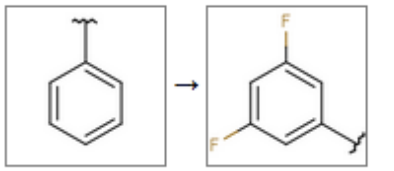
1 - 5 of 9 5 items on page 1 of 2 > >>



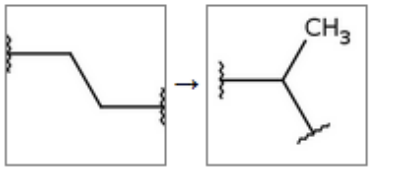
9 matched pairs
Δ mean = -0.79 ± 0.22
SMIRKS: FC1=CC=CC(F)=C1* ->
*C1=C(Cl)C=CC=C1Cl



9 matched pairs
Δ mean = -0.32 ± 0.19
SMIRKS: *N* -> *O*



16 matched pairs
Δ mean = 0.33 ± 0.12
SMIRKS: *C1=CC=CC=C1 ->
FC1=CC(*)=CC(F)=C1

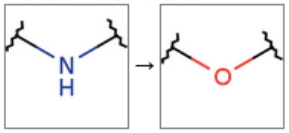


9 matched pairs
Δ mean = 0.43 ± 0.18
SMIRKS: *CC* -> CC(*)*

MMPs for quantitative activity data

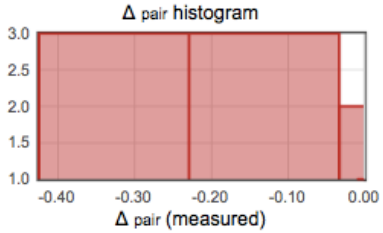
The info is based on dataset **ic50_RT HIV** for property **IC50 HIV**
Minimal pair similarity: 50

Transformation details:



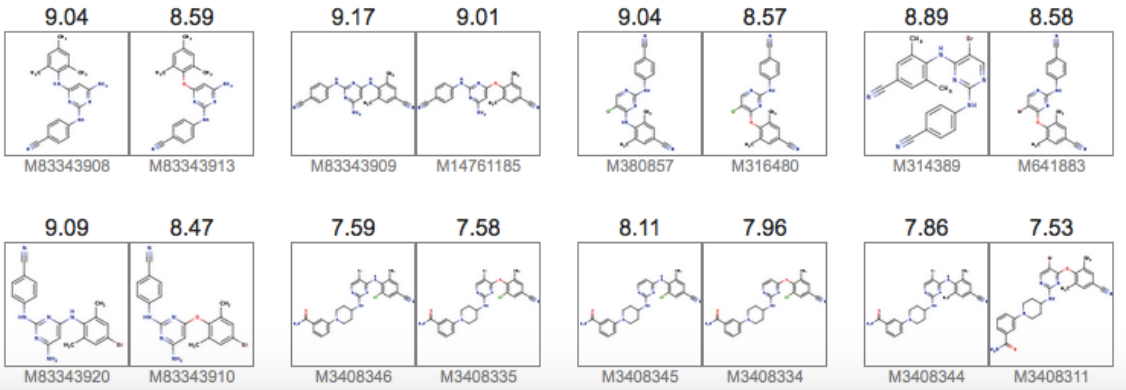
Transformation ID: TR 5719
SMIRKS: *N* -> *O*

Back to all transformations



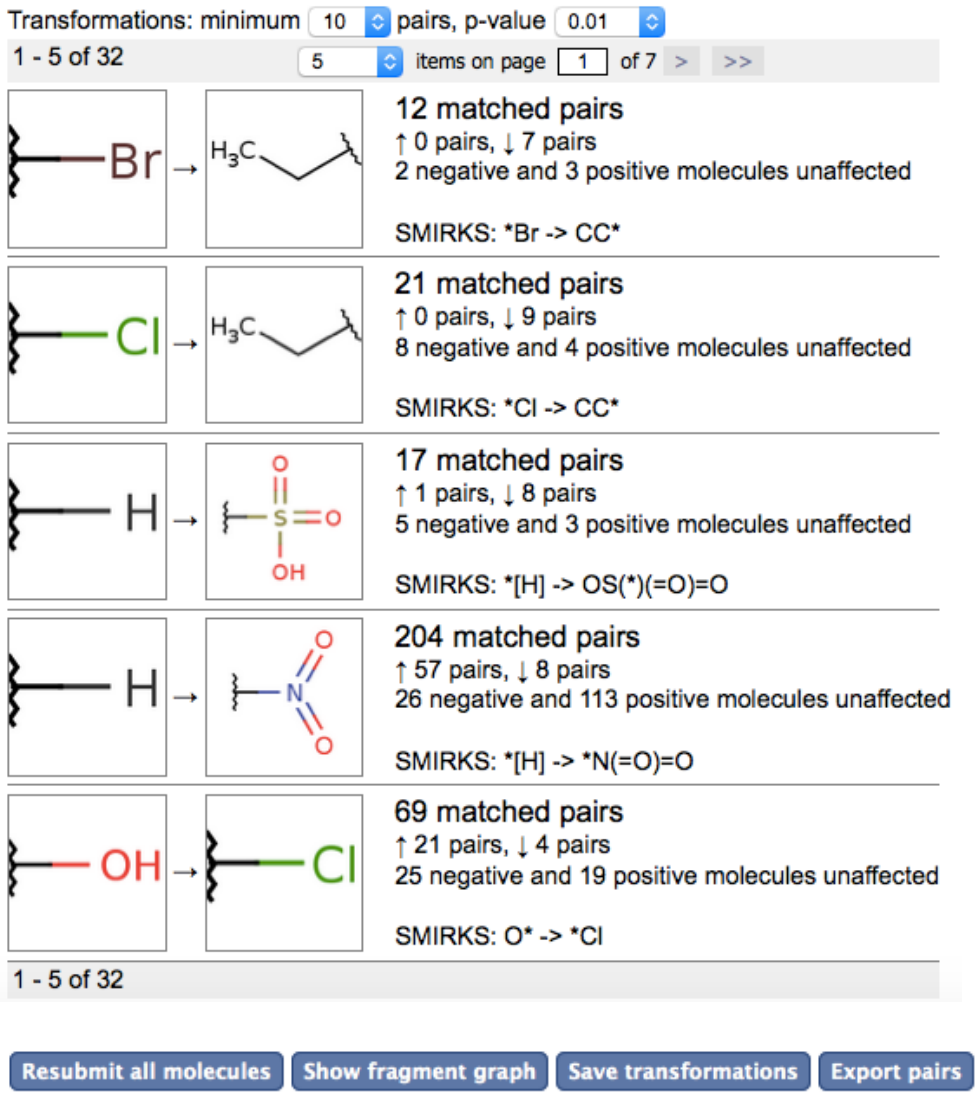
Pairs having the same transformation as the selected one:

1 - 9 of 9

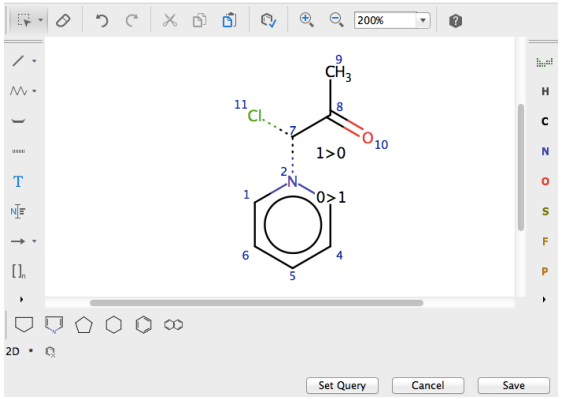


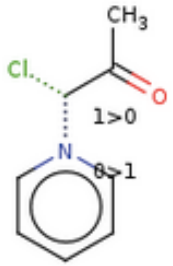
Resubmit all molecules | Show fragment graph | Save transformations | Export pairs

MMPs for classification data (AMES mutagenicity)



Storage of Chemical Reaction as Condensed Graph of Reaction (CRG)





molecule profile

● SN2 reaction

rate constant =

-4.72 (in log(L*mol^(-1)*s^(-1)))

Nugmanov, R. et al

Development of "structure-property" models in nucleophilic s...

N: 8 P: 270

Journal of Structural Chemistry **2014**; 55 (6) 1026-1032

MoleculeID: *M84326300*

Private record

Temperature= 55.6 °C

Solvent = Ethanol

RecordID: *R19277000*

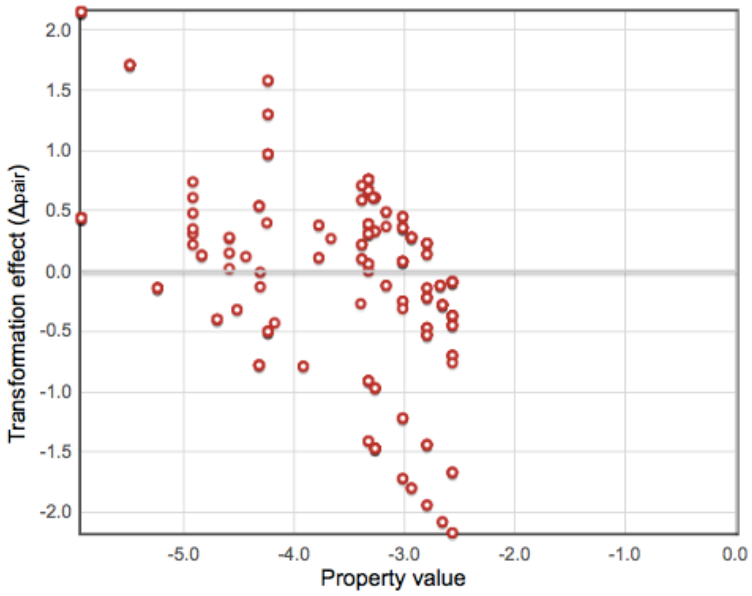
23:25, 4 Jul 15 / 20:32, 6 Jul 15

itetko

Only visible to itetko

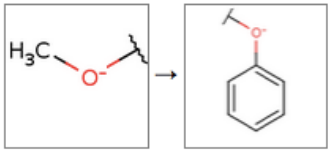
MMPs for CGRs

The info is based on dataset **methanol - 25** for property **SN2 reaction rate constant** (excluding 15 molecules not indexed for MMP analysis)
Minimal pair similarity: 50

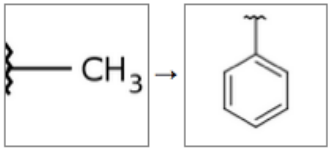


MMP transformations: minimum 2 pairs, p-value Any, max. atoms Any

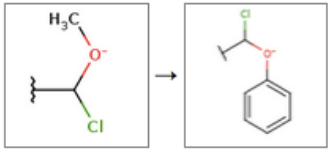
1 - 5 of 22 | 5 items on page | 1 of 5 > >>



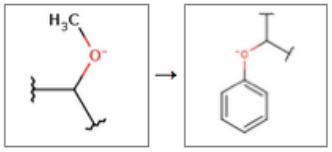
2 matched pairs
Δ mean = -0.59 ± 0.27
SMIRKS: [CH3:12][O-:13]* -> *[O-:8][C:13]1=[CH:12][CH:11]=[CH:10][CH:15]=[CH:14]1



2 matched pairs
Δ mean = -0.59 ± 0.27
SMIRKS: C* -> *C1=CC=CC=C1



2 matched pairs
Δ mean = -0.59 ± 0.27
SMIRKS: [CH3:9][O-:8][CH:7](*)[Cl:11] -> *[CH:7]([Cl:19])[O-:8][C:13]1=[CH:12][CH:11]=[CH:10][CH:15]=[CH:14]1

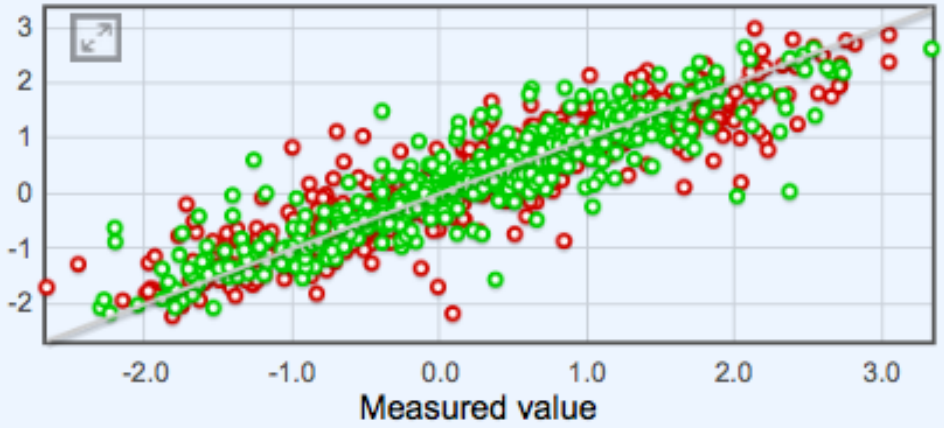


2 matched pairs
Δ mean = -0.59 ± 0.27
SMIRKS: [CH3:6][O-:5][CH:4](*)* -> *[CH:7](*)[O-:8][C:13]1=[CH:12][CH:11]=[CH:10][CH:15]=[CH:14]1

Regression Model for environmental toxicity

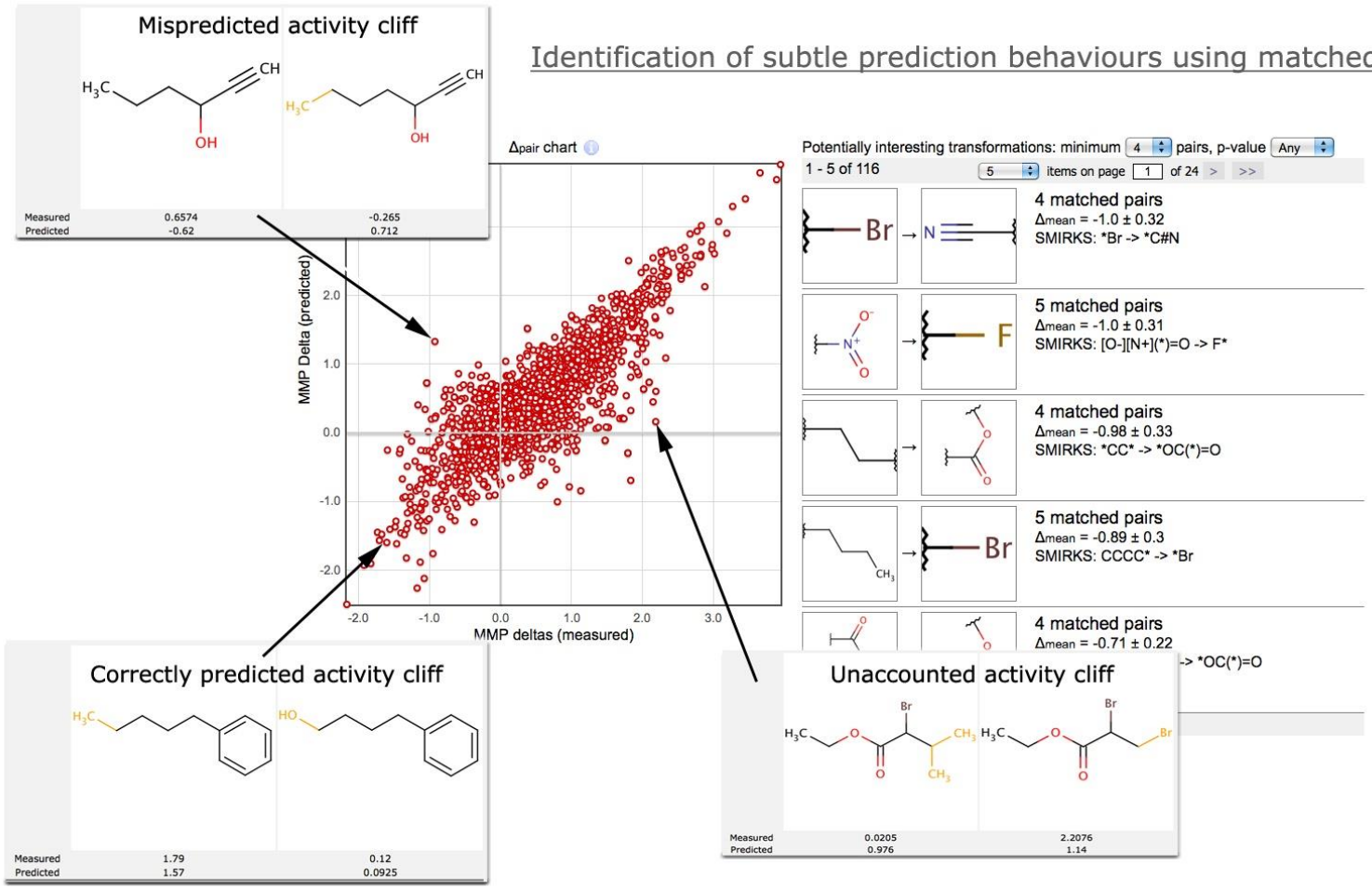
Predicted property: **log(IGC50-1)** modeled in -log(mmol/L)
Training method: ASNN

Data Set	#	R^2	q^2	RMSE	MAE
Training set: T. pyriformis train	644 records	0.83 ± 0.02	0.83 ± 0.02	0.44 ± 0.02	0.31 ± 0.01
Test set: T. pyriformis test [x]	449 records	0.81 ± 0.02	0.8 ± 0.02	0.46 ± 0.03	0.32 ± 0.02



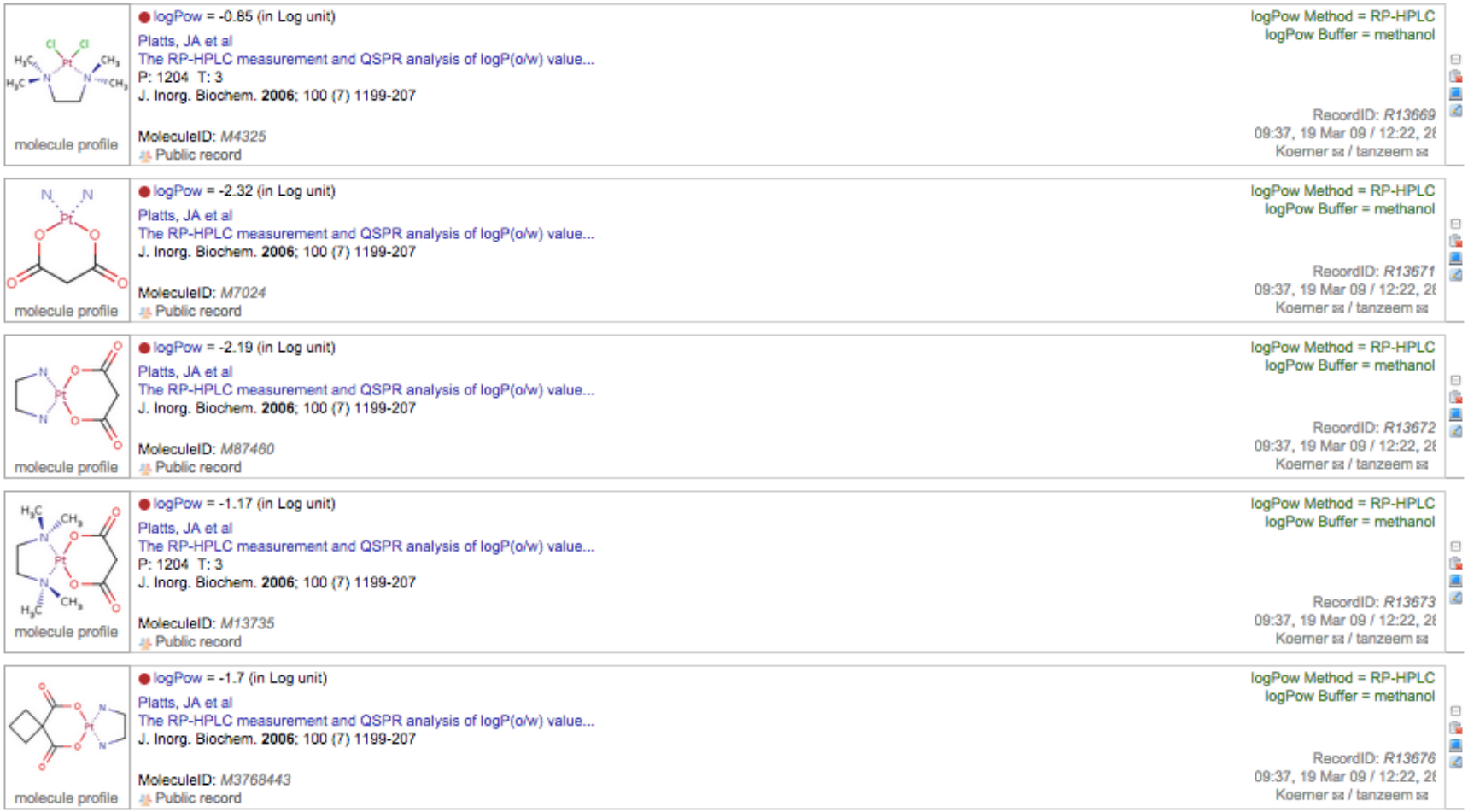
Download model statistics View configuration XML Export configuration XML MMP-based analysis

Identification of predicted MMPs



Sushko et al Prediction-Driven Matched Molecular Pairs to Interpret QSARs and Aid the Molecular Optimization Process. *J. Cheminformatics* 2014, 6 (1), 48. https://doi.org/10.1186/s13321-014-0048-0.

LogP of Pt(II) + Pt(IV) complexes

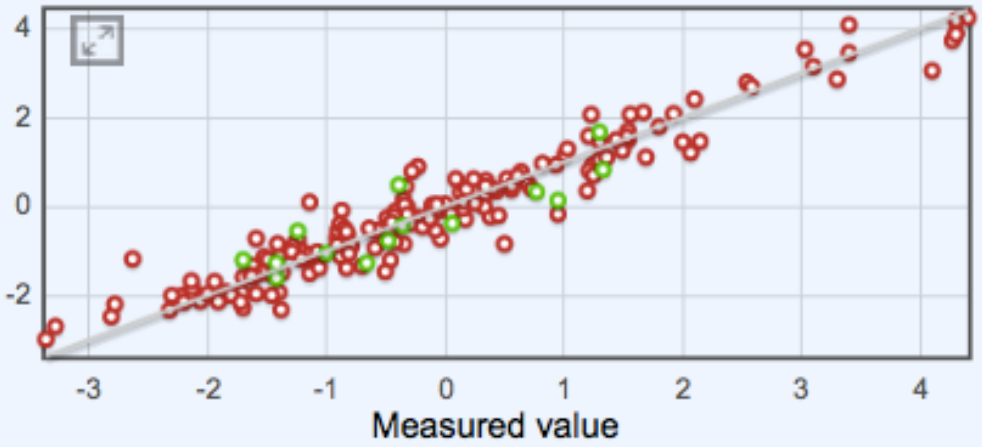


Tetko et al. Prediction of logP for Pt(II) and Pt(IV) Complexes: Comparison of Statistical and Quantum-Chemistry Based Approaches. J. Inorg. Biochem. 2016, 156, 1–13. https://doi.org/10.1016/j.jinorgbio.2015.12.006.

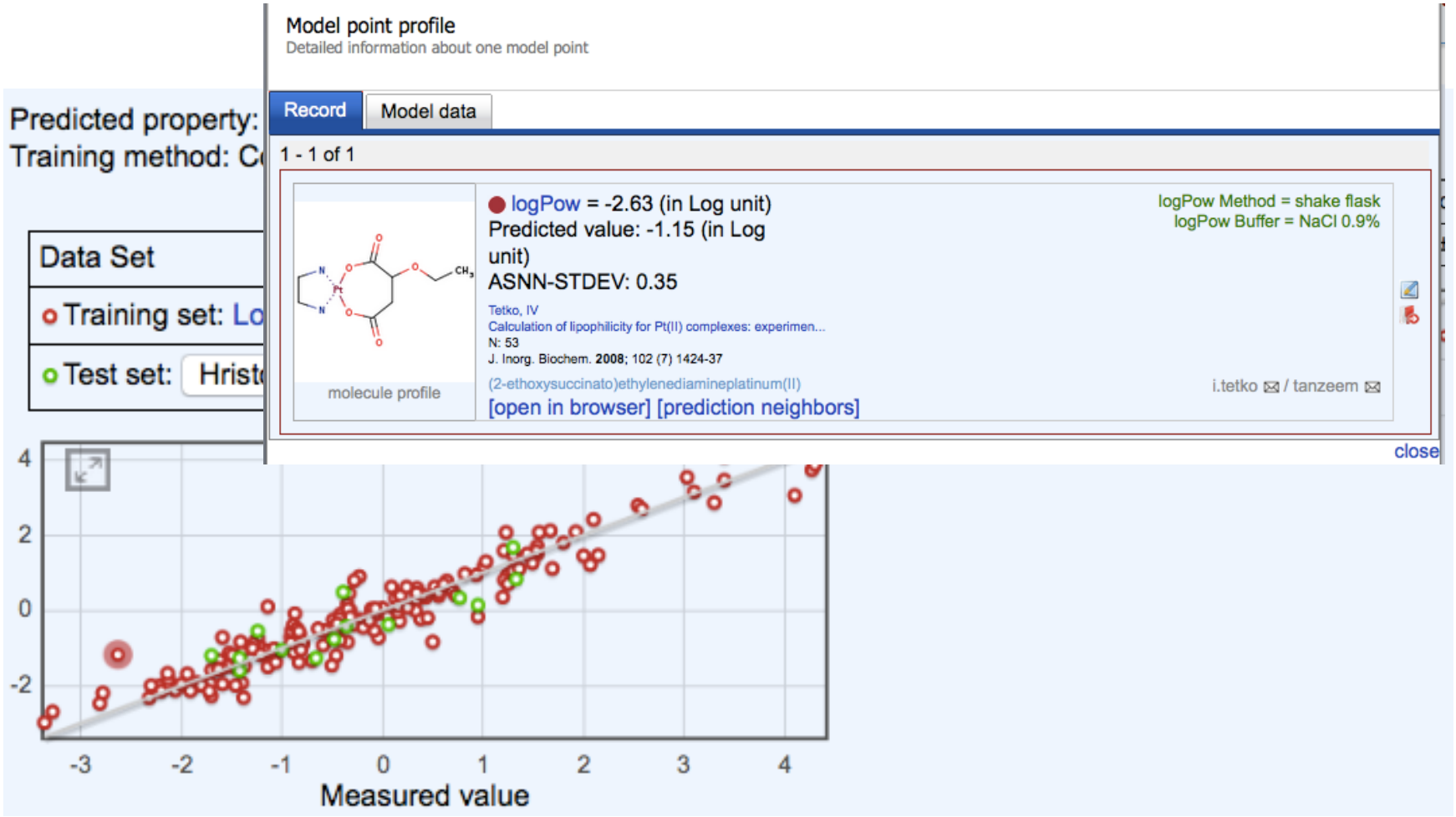
Model for LogP for Pt complexes

Predicted property: **logPow**
Training method: Consensus

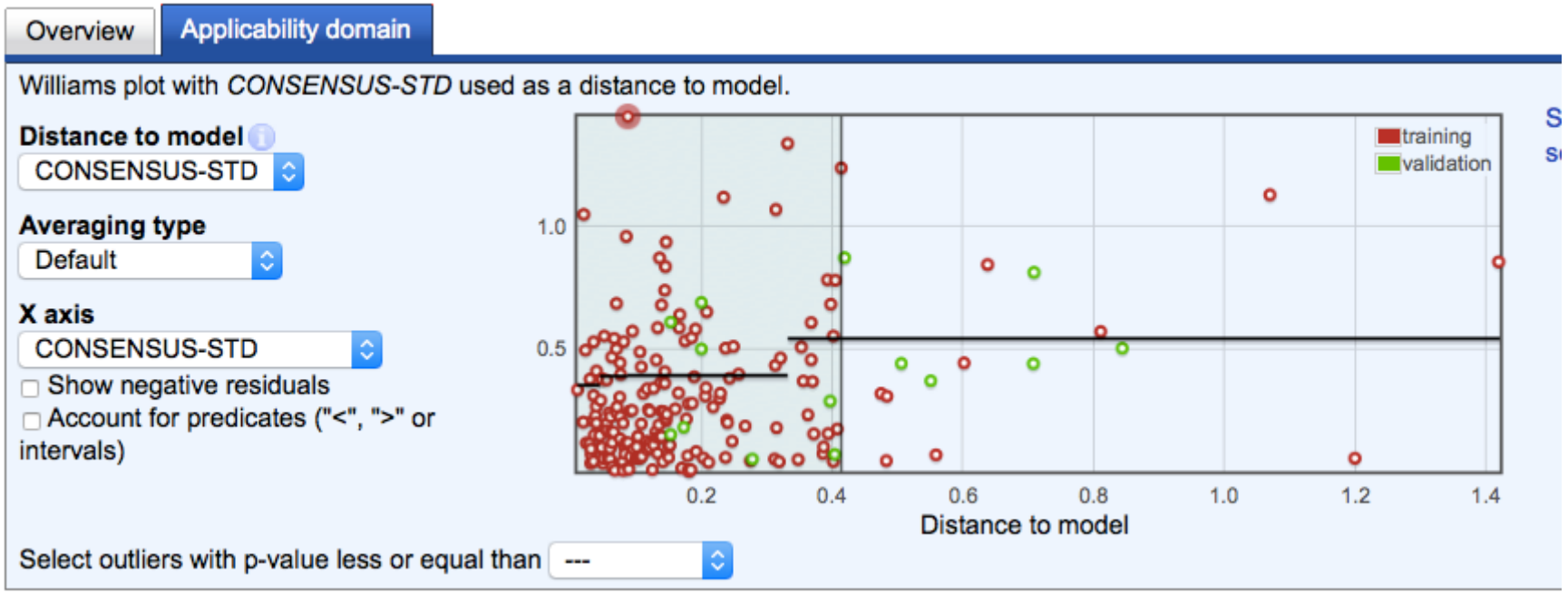
Data Set	#	R2	q2	RMSE	MAE
Training set: LogPt final	187 records	0.93 ± 0.01	0.93 ± 0.01	0.41 ± 0.03	0.3 ± 0.02
Test set: Hristo [x]	14 records	0.76 ± 0.1	0.76 ± 0.1	0.5 ± 0.06	0.43 ± 0.07



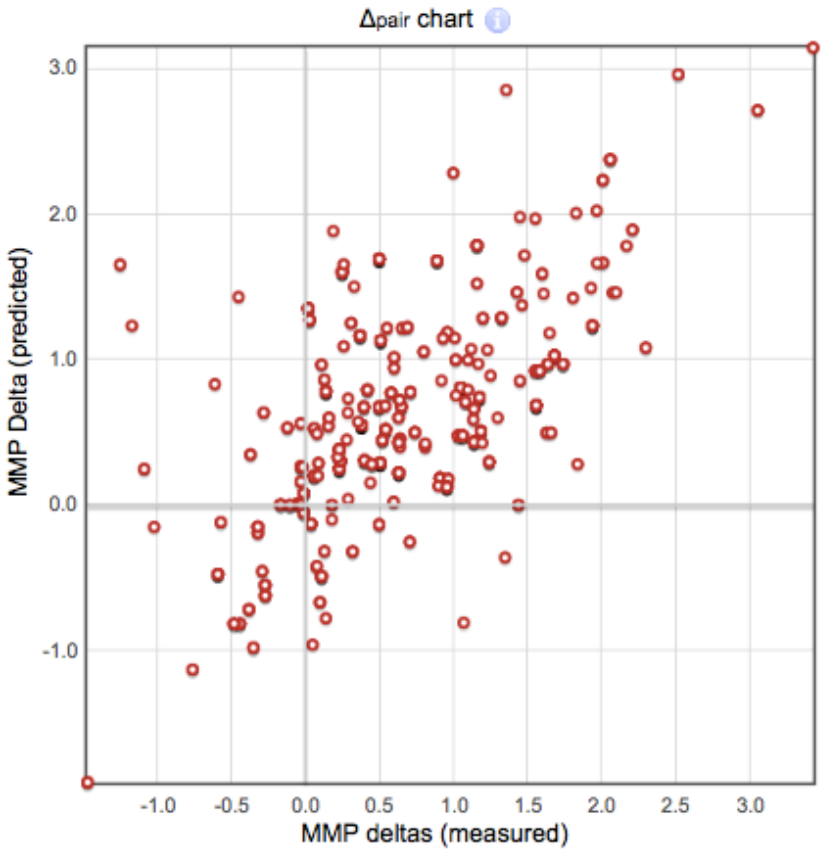
Model for LogP for Pt complexes



Outlying point on the Applicability Domain plot

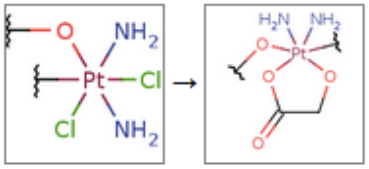


Prediction of logP for Pt complexes

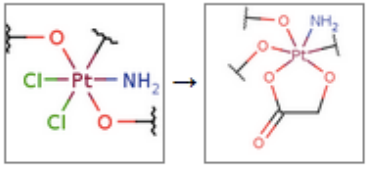


Transformations: minimum 4 pairs, p-value Any

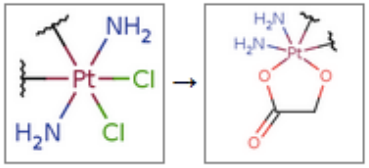
1 - 5 of 60 5 items on page 1 of 12 > >>



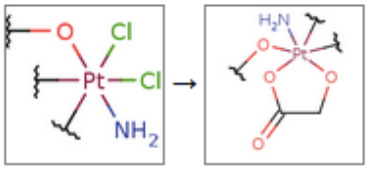
6 matched pairs
Δmean = -0.27 ± 0.19
SMIRKS: N[Pt](N)(*)(Cl)(Cl)O* -> N[Pt]1(N)(*)(O*)OCC(=O)O1



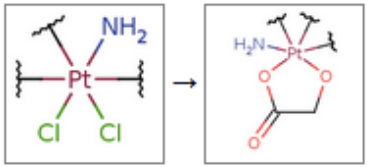
6 matched pairs
Δmean = -0.27 ± 0.19
SMIRKS: N[Pt](*)(Cl)(Cl)(O*)O* -> N[Pt]1(*)(O*)(O*)OCC(=O)O1



7 matched pairs
Δmean = -0.24 ± 0.2
SMIRKS: N[Pt](N)(*)(*)(Cl)Cl -> N[Pt]1(N)(*)(*)OCC(=O)O1

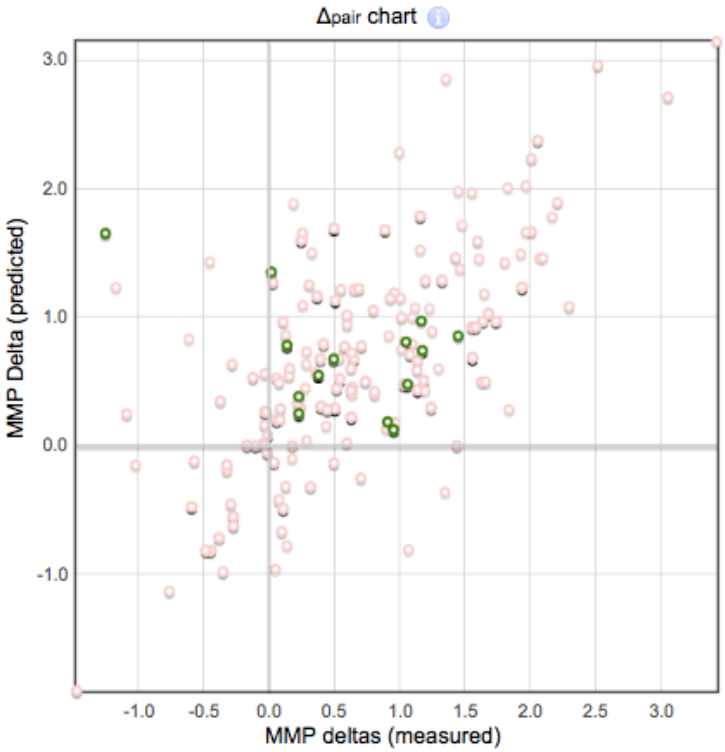


7 matched pairs
Δmean = -0.24 ± 0.2
SMIRKS: N[Pt](*)(*)(Cl)(Cl)O* -> N[Pt]1(*)(*)(O*)OCC(=O)O1

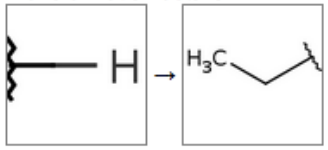


8 matched pairs
Δmean = -0.17 ± 0.26
SMIRKS: N[Pt](*)(*)(*)(Cl)Cl -> N[Pt]1(*)(*)(*)OCC(=O)O1

Outliers of the model (functional groups descriptors)

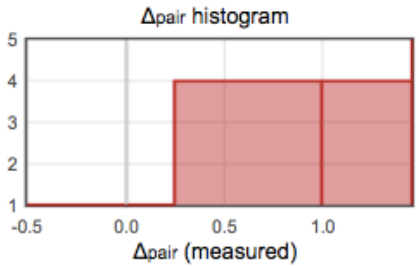


Transformation details:



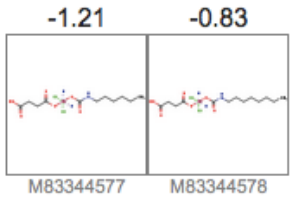
Transformation ID: TR181
SMIRKS: *[H] -> CC*

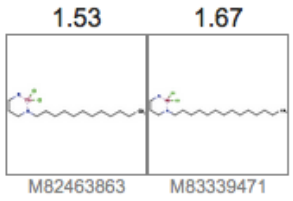
Back to all transformations

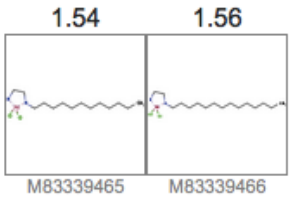


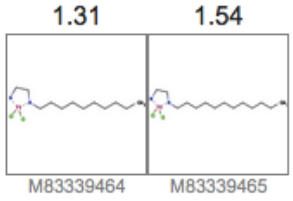
Pairs having the same transformation as the selected one:

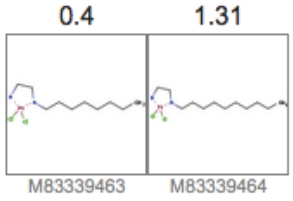
1 - 14 of 14

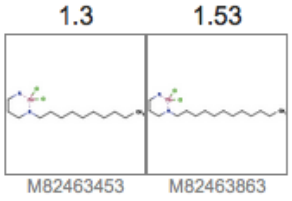




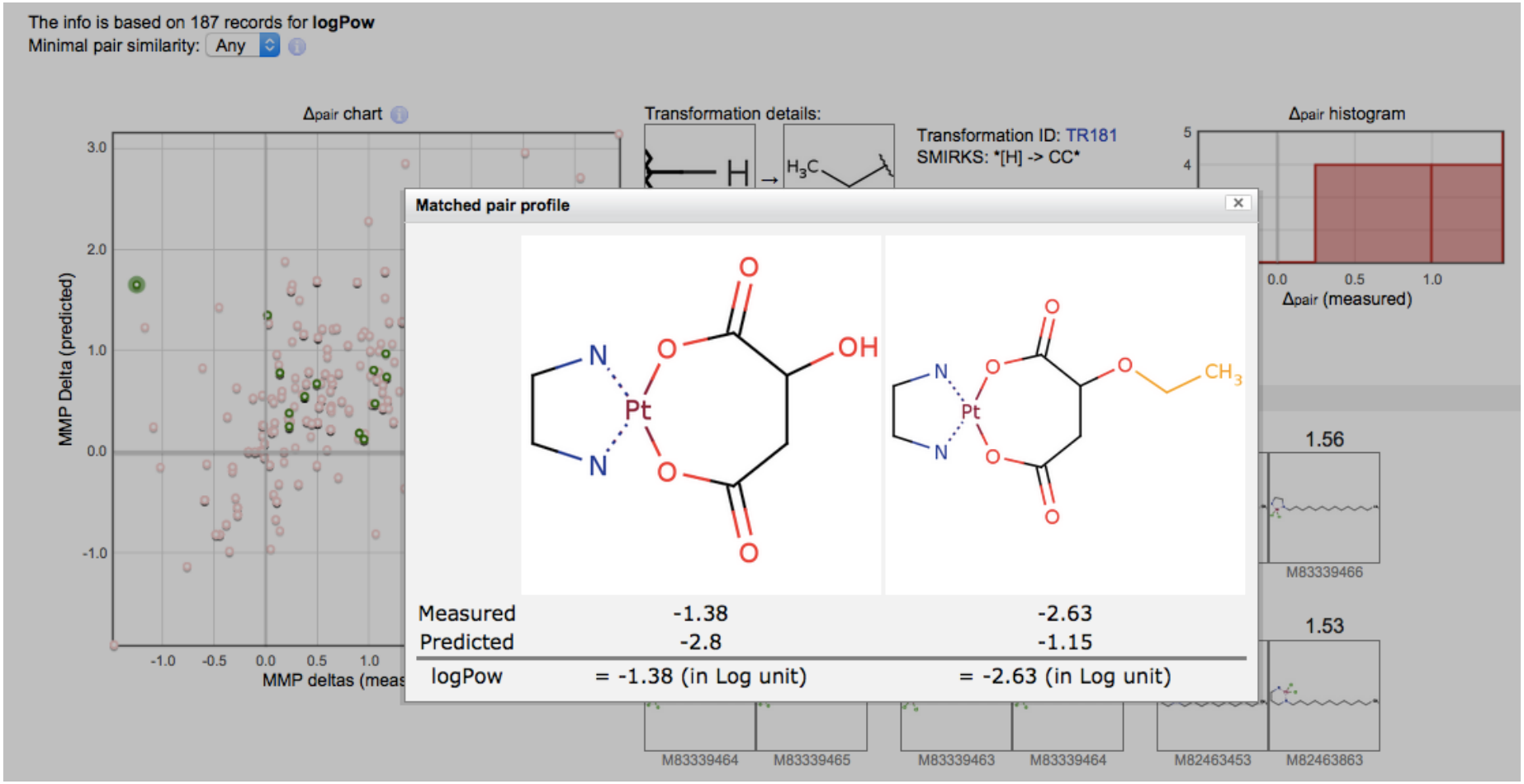




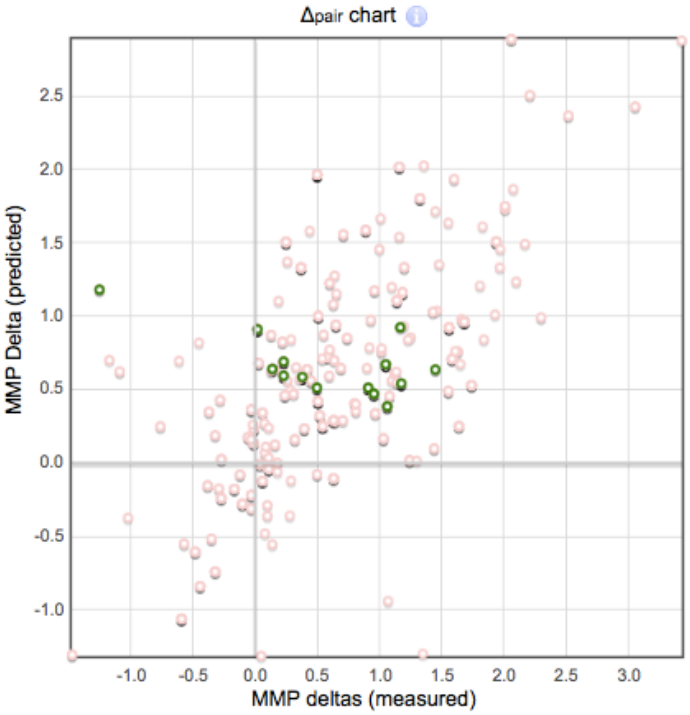




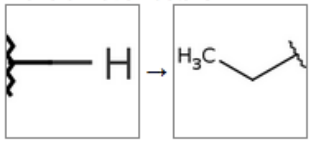
Outliers of the model (Functional groups descriptors)



Outliers of the model (CDK descriptors)

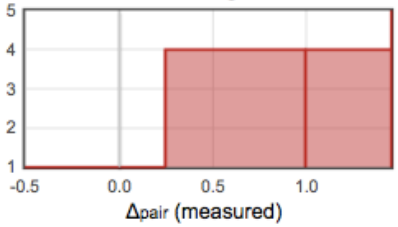


Transformation details:



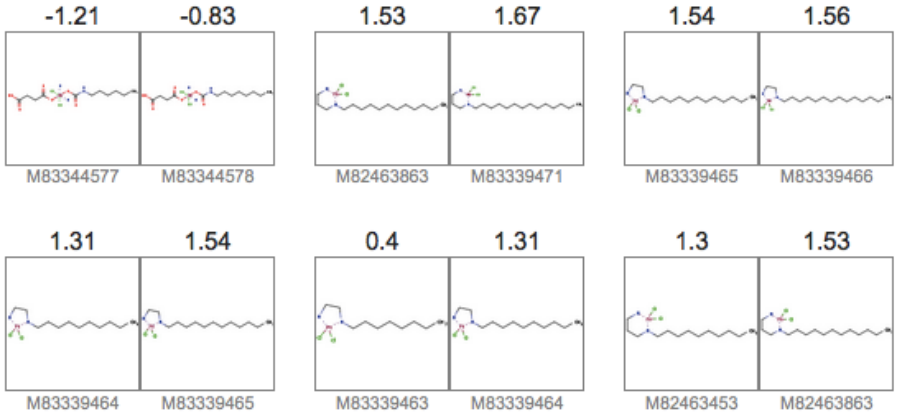
Transformation ID: TR181
SMIRKS: *[H] -> CC*

Back to all transformations

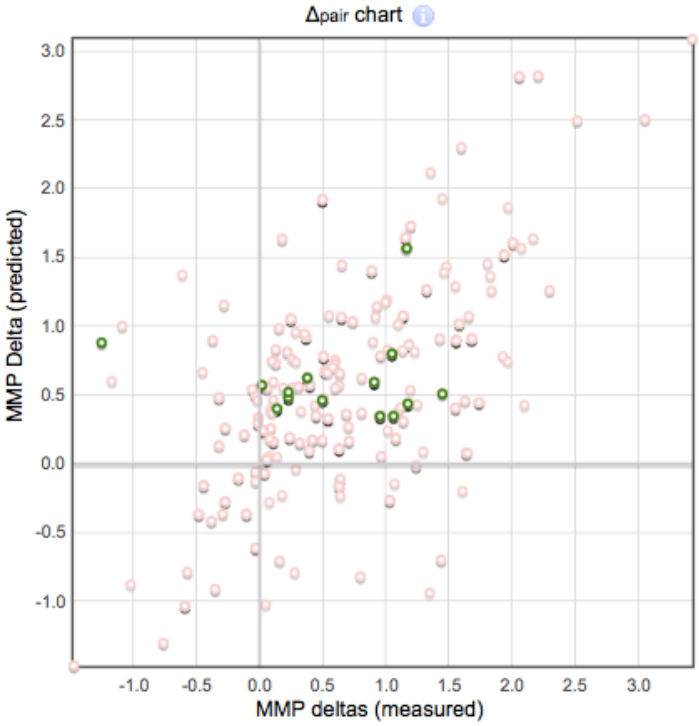


Pairs having the same transformation as the selected one:

1 - 14 of 14



Outliers of the model (Estate descriptors)



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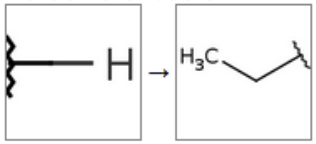
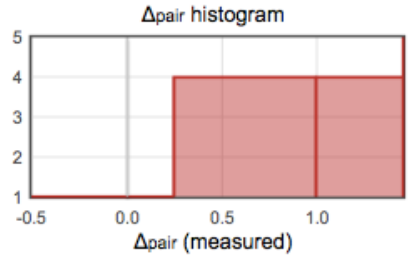


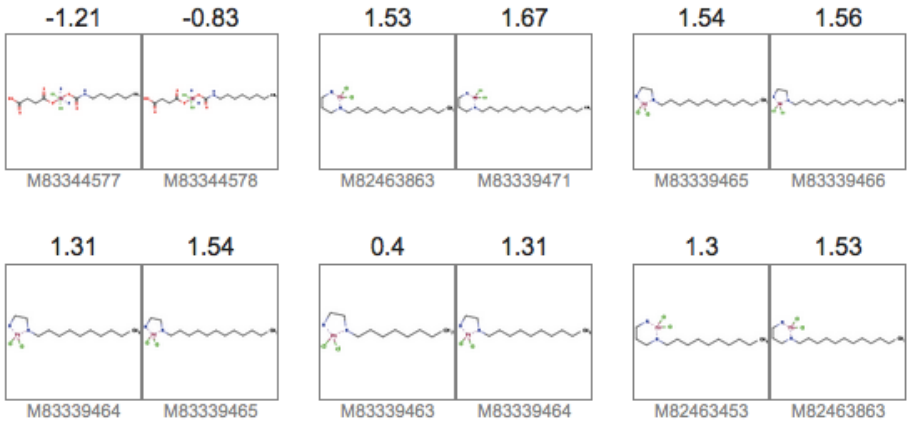
Transformation ID: TR181
SMIRKS: *[H] -> CC*

Back to all transformations



Pairs having the same transformation as the selected one:

1 - 14 of 14



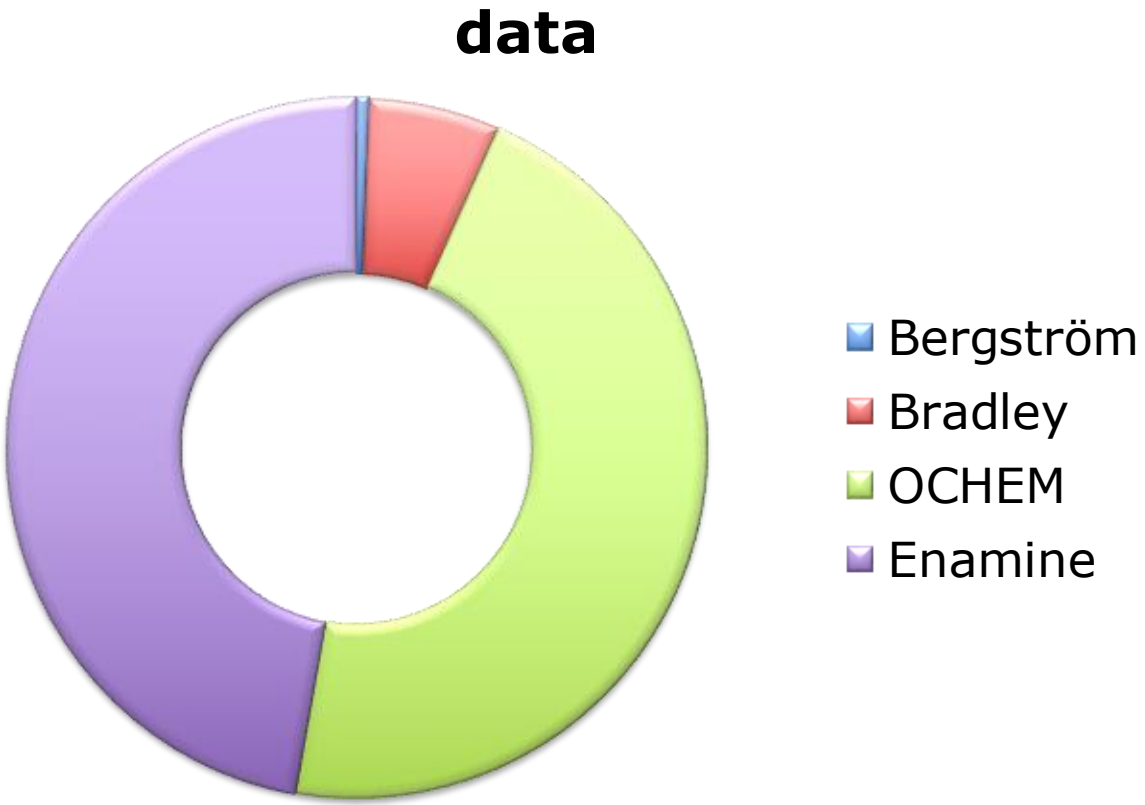
Model predictions (Bergström set)

Bergström 277

Bradley 2886

OCHEM 22404

Enamine 21883



Tetko et al *J. Chem. Inf. Model*. 2014, 22;54(12):3320-9.

Model predictions (Bergström set)

Method	RMSE	MAE	R^2
Estate	36 ± 2	31 ± 3	0.49 ± 0.09
Consensus	34 ± 1	26 ± 2	0.63 ± 0.07
Karthikeyan et al	41.4		0.66
Bergström et al	49.8		0.54
Nigsch et al	46.3		0.30
Hughes et al	52.8	40.7	0.46

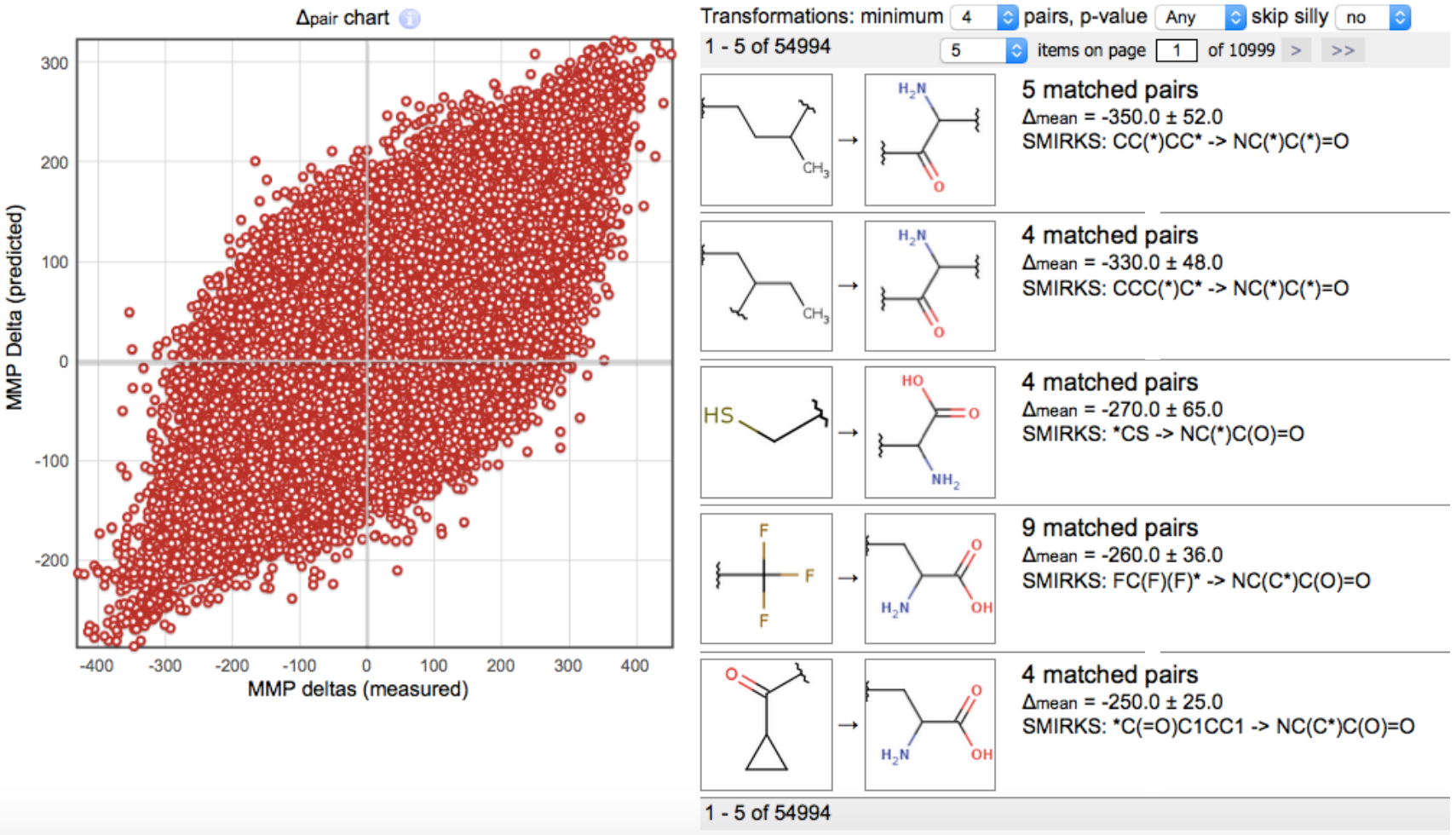
Bergstrom, et al *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1177-1185.

Karthikeyan, et al *J. Chem. Inf. Model.* **2005**, *45*, 581-590.

Nigsch, et al *J. Chem. Inf. Model.* **2006**, *46*, 2412-2422.
Hughes et al *J. Chem. Inf. Model.* **2008**, *48*, 220-232.

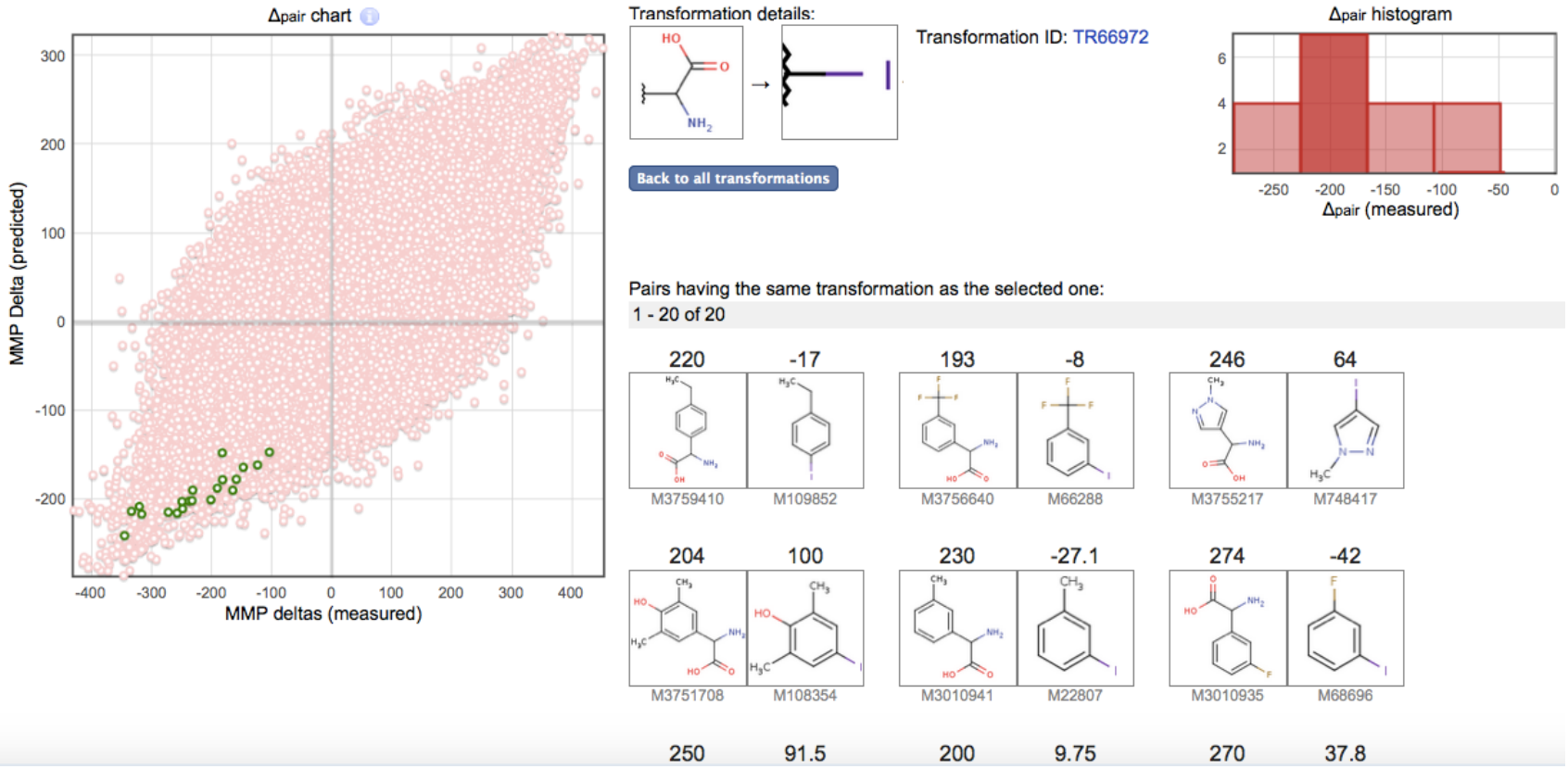
Tetko, I. V.; M Lowe, D.; Williams, A. J. The Development of Models to Predict Melting and Pyrolysis Point Data Associated with Several Hundred Thousand Compounds Mined from PATENTS. J. Cheminformatics **2016**, 8, 2. https://doi.org/10.1186/s13321-016-0113-y.

Predicted MMPs for Melting Point



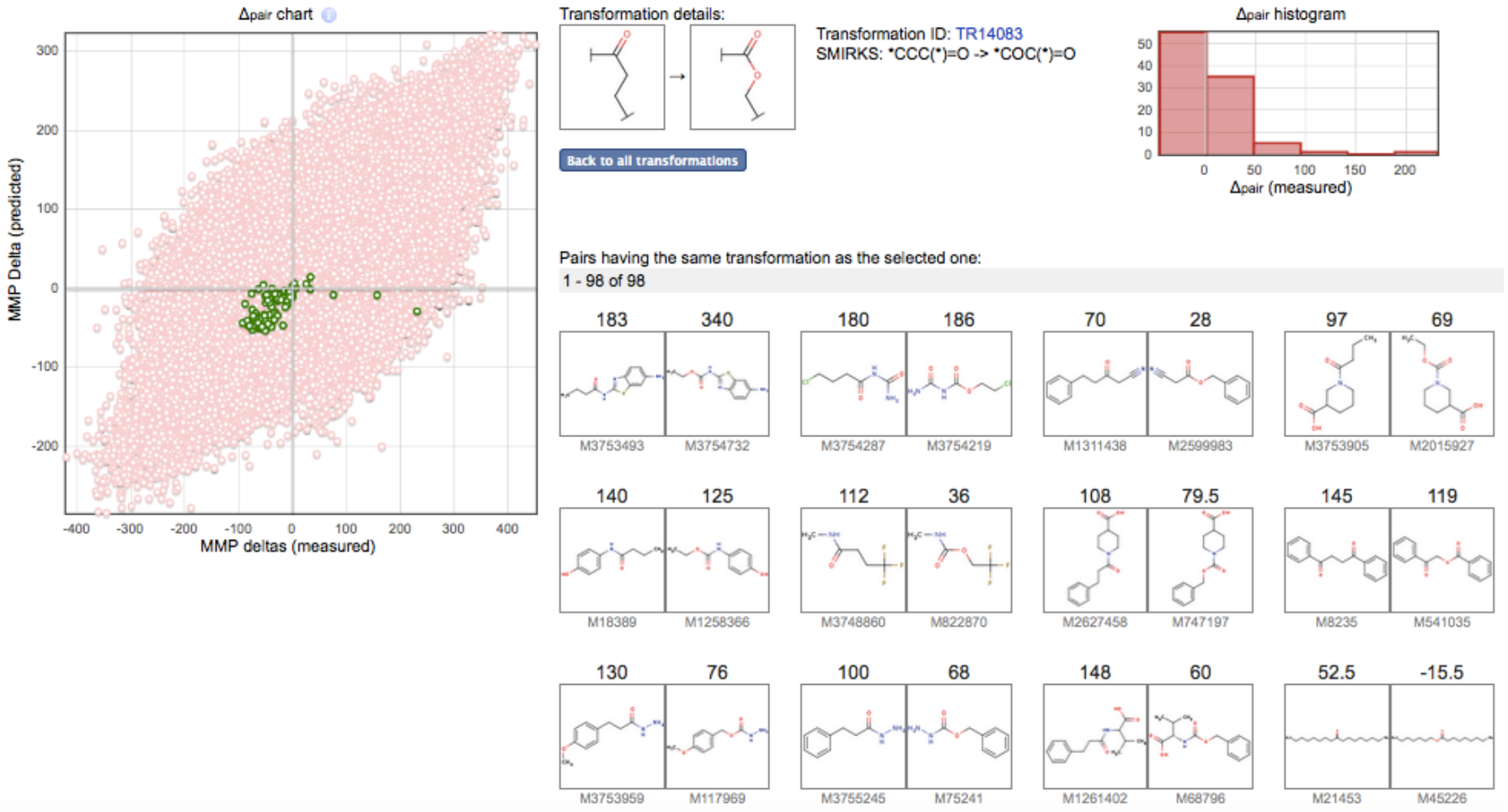
Withnall, M.; Chen, H.; Tetko, I. V. Matched Molecular Pair Analysis on Large Melting Point Datasets: A Big Data Perspective. *ChemMedChem* **2018**, 13 (6), 599–606. https://doi.org/10.1002/cmdc.201700303.

An example of MMP transformation



Withnall, M.; Chen, H.; Tetko, I. V. Matched Molecular Pair Analysis on Large Melting Point Datasets: A Big Data Perspective. *ChemMedChem* **2018**, 13 (6), 599–606. https://doi.org/10.1002/cmdc.201700303.

An example of MMP transformation



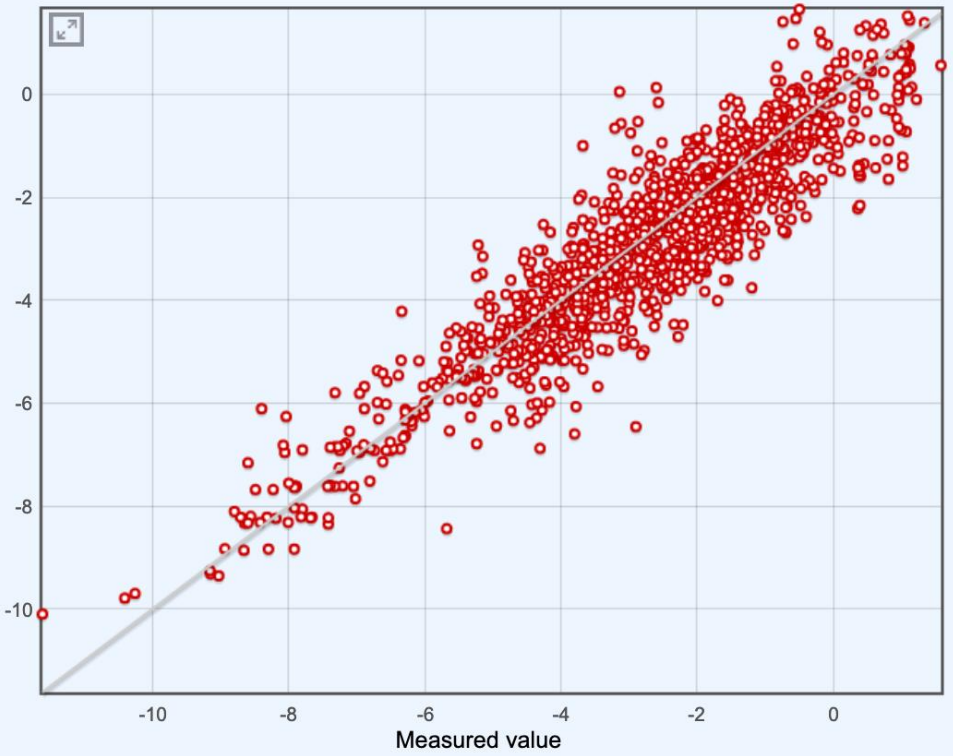
Withnall, M.; Chen, H.; Tetko, I. V. Matched Molecular Pair Analysis on Large Melting Point Datasets: A Big Data Perspective. *ChemMedChem* **2018**, 13 (6), 599–606. https://doi.org/10.1002/cmdc.201700303.

Prediction of solubility using Yalkowsky's equation

logS = 0.5 – 0.01(MP-25) – logP

Predicted property: **Aqueous Solubility** modeled in log(mol/L)
Training method: MLRA

Data Set	#	R^2	q^2	RMSE	MAE
Training set: ALOGPS 2.1 logS (training)	1311 records	0.842 ± 0.01	0.83 ± 0.01	0.84 ± 0.02	0.64 ± 0.02



Download descriptors and model statistics View configuration XML Export configuration XML

Conclusions

- OCHEM is powerful platform for model development
- It provides best strategies for model development
- Cautions should be taken to avoid overfitting
- Validation techniques should match intended model use
- Use interpretable descriptors to interpret models
- MMP are useful for model interpretation

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Katya Ahmad
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BigChem

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