BIGCHEM, online lecture, 7 Febuary 2018

Interpretation of QSAR models

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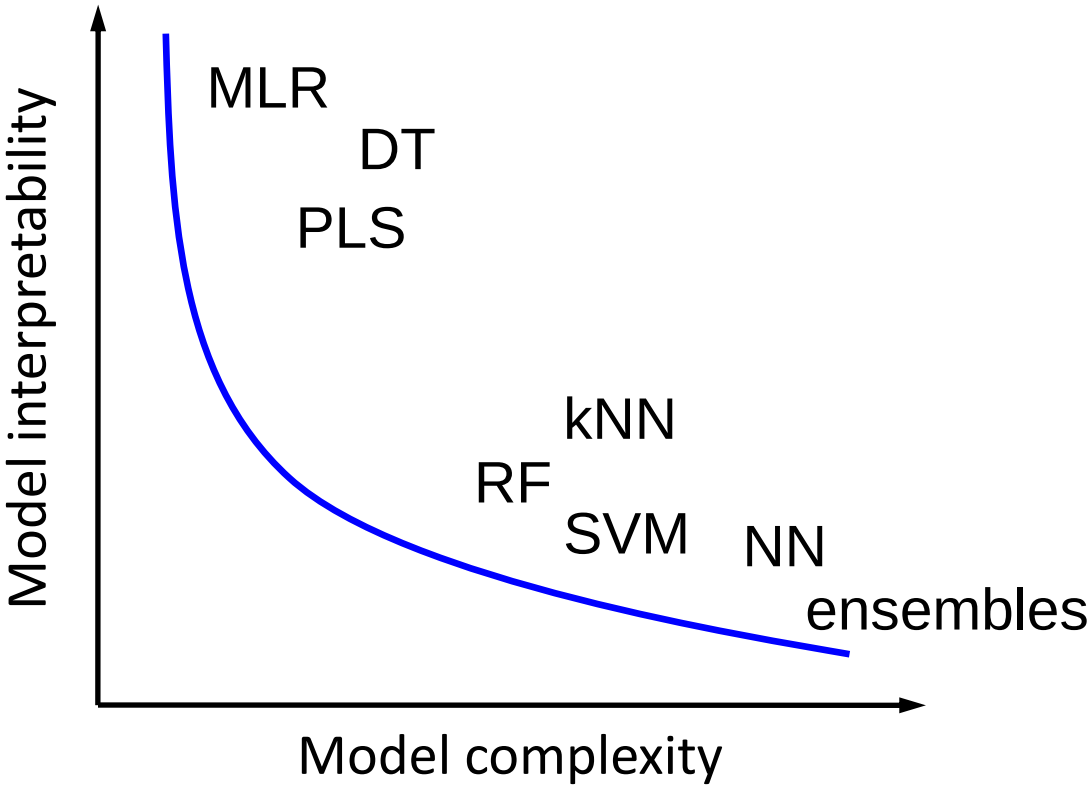
Outline

1. Introduction. Importance, principles and issues of interpretation of QSAR models. Global and local interpretation.
2. “Model → descriptor → (structure)” interpretation paradigm
   a) Machine learning-specific interpretation approaches
   b) Machine learning-independent interpretation approaches
3. “Model → structure” interpretation paradigm
4. Context dependence of interpretation results
5. Interpretability of data sets
6. Conclusion

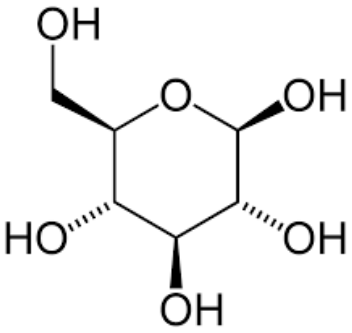
Interpretability vs. predictivity of QSAR models

Popular misbelief

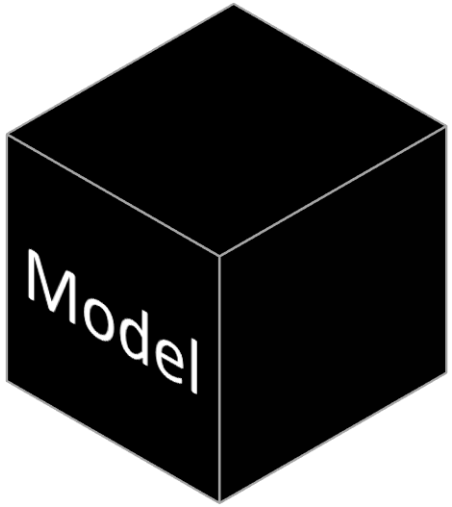


Machine learning

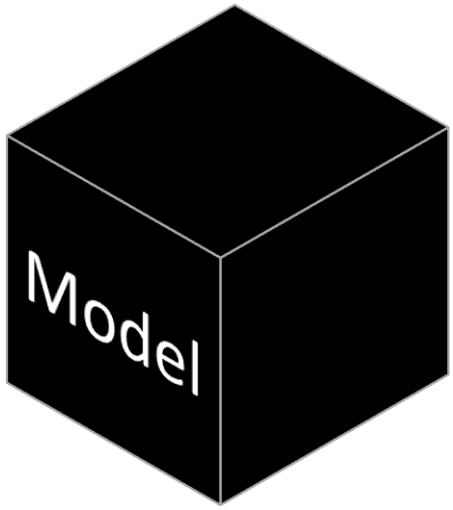
Conventional learning



D_1	D_2	D_3	...	D_N
1	0	9	...	1
4	0	1	...	1
0	2	3	...	3
...	...	...	...	...
4	0	0	...	1



Output



Representative learning

Why interpretation is important?

Found active/inactive patterns which can be used for optimization of compound properties

Retrieve trends of stricture-activity relationships which can be used for knowledge-base model validation and for better understanding of the studied end-point (formulate hypothesis)

Regulatory purposes

OECD principles for the validation, for regulatory purposes, of (Q)SAR models

1) a defined endpoint
2) an unambiguous algorithm
3) a defined domain of applicability
4) appropriate measures of goodness-of–fit, robustness and predictivity
5) a mechanistic interpretation, if possible

Interpretation of QSAR models: principles and issues

Model should be predictive

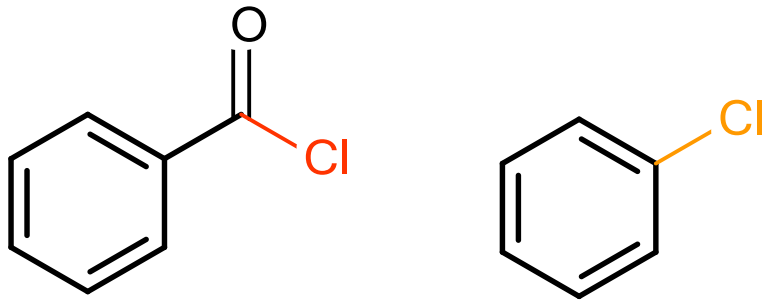
Interpretation is valid within the applicability domain of the model

Interpretation results are data set dependent

Local vs. global interpretation

Local interpretation

considers mutual influence of atoms (fragments) in a single compound



Global interpretation

summarizes interpretation results across studied compounds to reveal general structure-activity relationship trends

$$F \rightarrow Cl \rightarrow Br \rightarrow I$$

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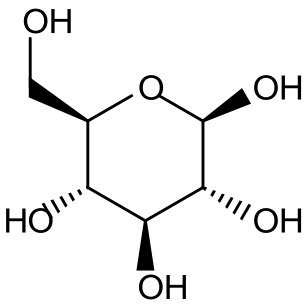
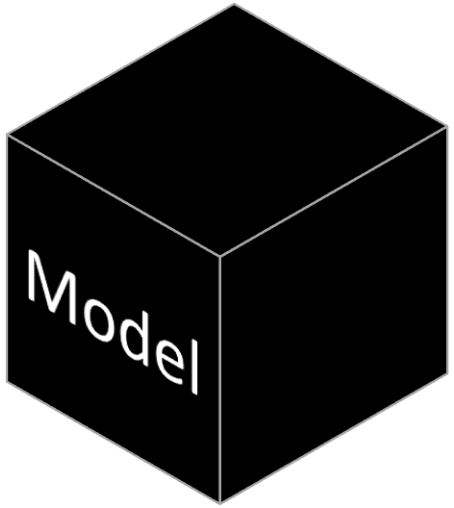
Learning and interpretation

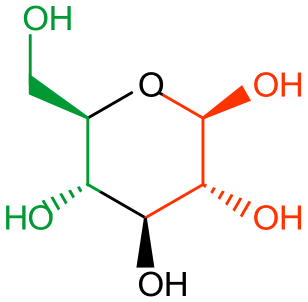
Learning



D_1	D_2	D_3	...	D_N
1	0	9	...	1
4	0	1	...	1
0	2	3	...	3
...	...	...	...	...
4	0	0	...	1



Output



(optional)

Descriptor contributions

Interpretation

“model → descriptor → (structure)” paradigm

“model → descriptor → (structure)” paradigm

Machine learning-specific interpretation approaches

- Linear models (LR, PLS, OPLS, etc)
- Decision tree
- Random Forest
- Neural nets
- Support vector machine
- Rule-extraction

Machine learning-independent interpretation approaches

- Variable importance
- Sensitivity analysis
- Partial derivatives

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Hansch approach

plant growth inhibition activity of phenoxyacetic acids

$$1/C = 4.08\pi - 2.14\pi^2 + 2.78\sigma + 3.38$$

rate of penetration of membranes in the plant cell

electronic factors

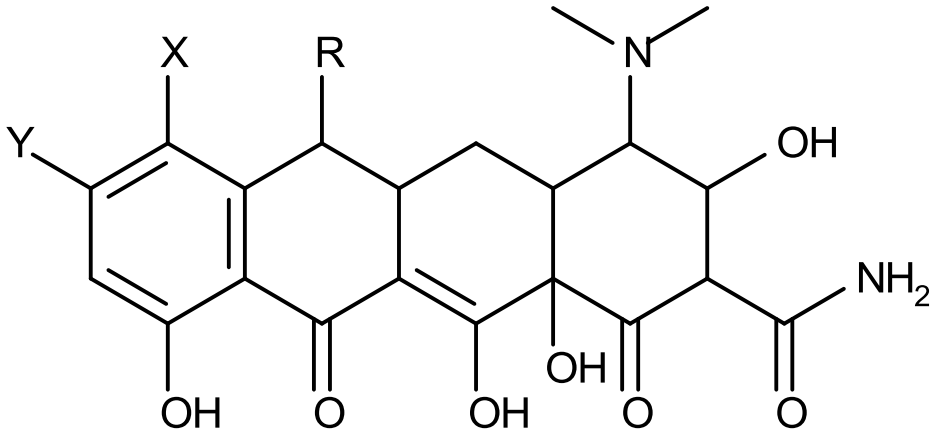
$$\pi = \log P_X - \log P_H$$

σ - Hammet constant

Hansch, C.; Maloney, P. P.; Fujita, T.; Muir, R. M. *Nature* **1962,** *194*, 178-180

Free and Wilson approach

Inhibition activity of compounds against *Staphylococcus aureus*



R is H or CH_3;
X is Br, Cl, NO_2 and
Y is NO_2, NH_2, $NHC(=O)CH_3$

$$Act = 75R_H - 112R_{CH3} + 84X_{Cl} - 16X_{Br} - 26X_{NO2} + 123Y_{NH2} + 18Y_{NHC(=O)CH3} - 218Y_{NO2}$$

Free, S. M.; Wilson, J. W. *Journal of Medicinal Chemistry* **1964,** *7*, 395-399

Interpretation of decision tree models

Solid-phase fluorescence enhancement of 2-(diphenylacetyl)-1,3-indandione 1-(p-(dimethylamino)benzaldazine)

ANALYTICAL CHEMISTRY, VOL. 57, NO. 9, AUGUST 1985 • 1953

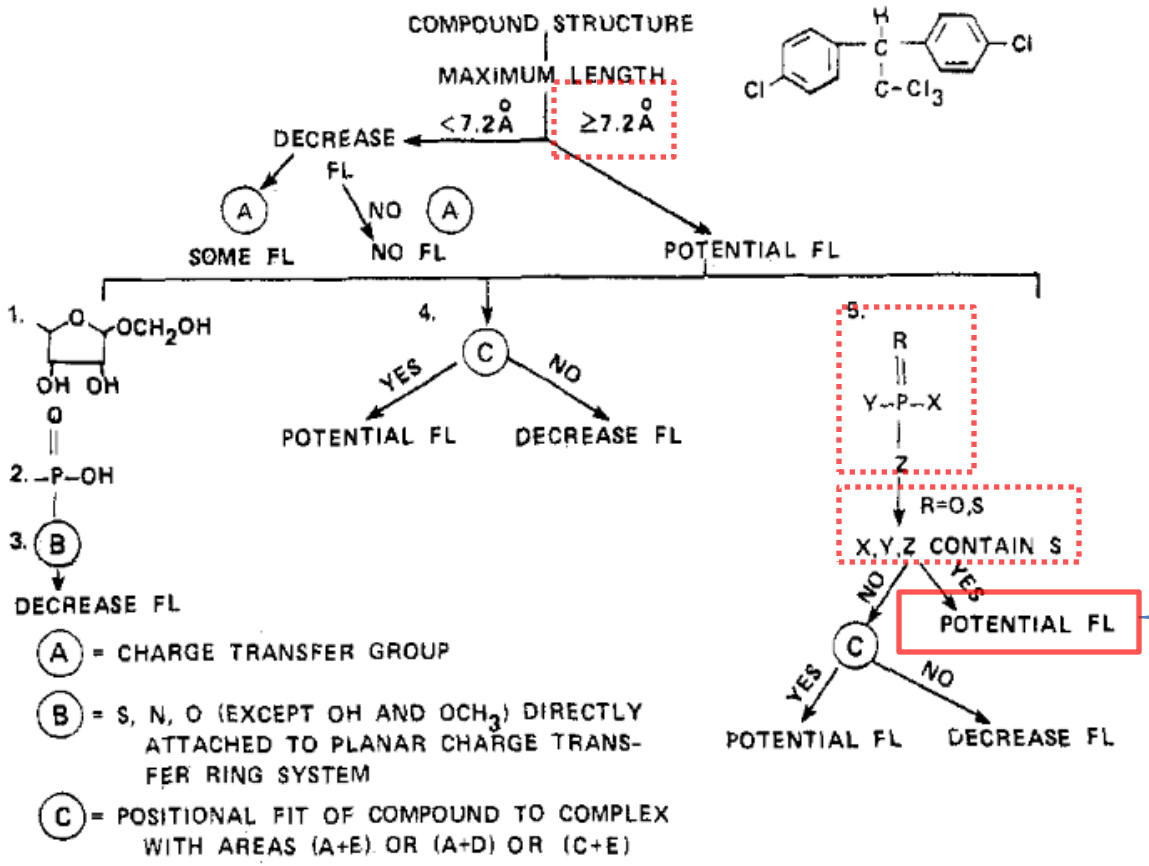


Figure 5. Decision tree: compound/II fluorescence enhancement.

1) the maximum length ≥ 7.2Å

AND

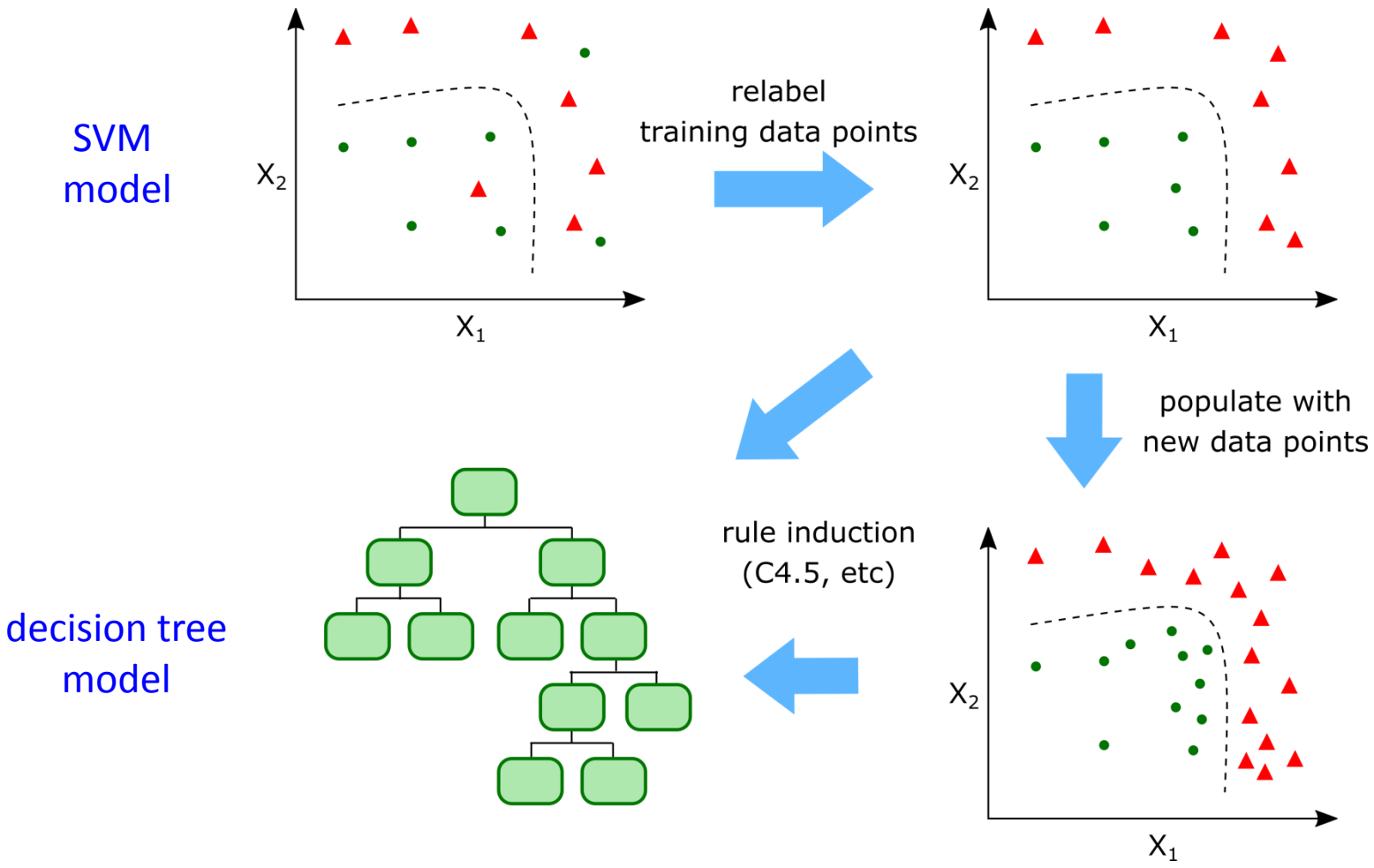
2) pentavalent phosphorous atom P(=R)(-X)(-Y)-Z is present where R is O or S

AND

3) X, Y, Z contain S

Ashman, W.P., Lewis, J.H., Poziomek, E.J., Analytical Chemistry, **1985**, 57(9): p. 1951-1955.

Rule-extraction approaches

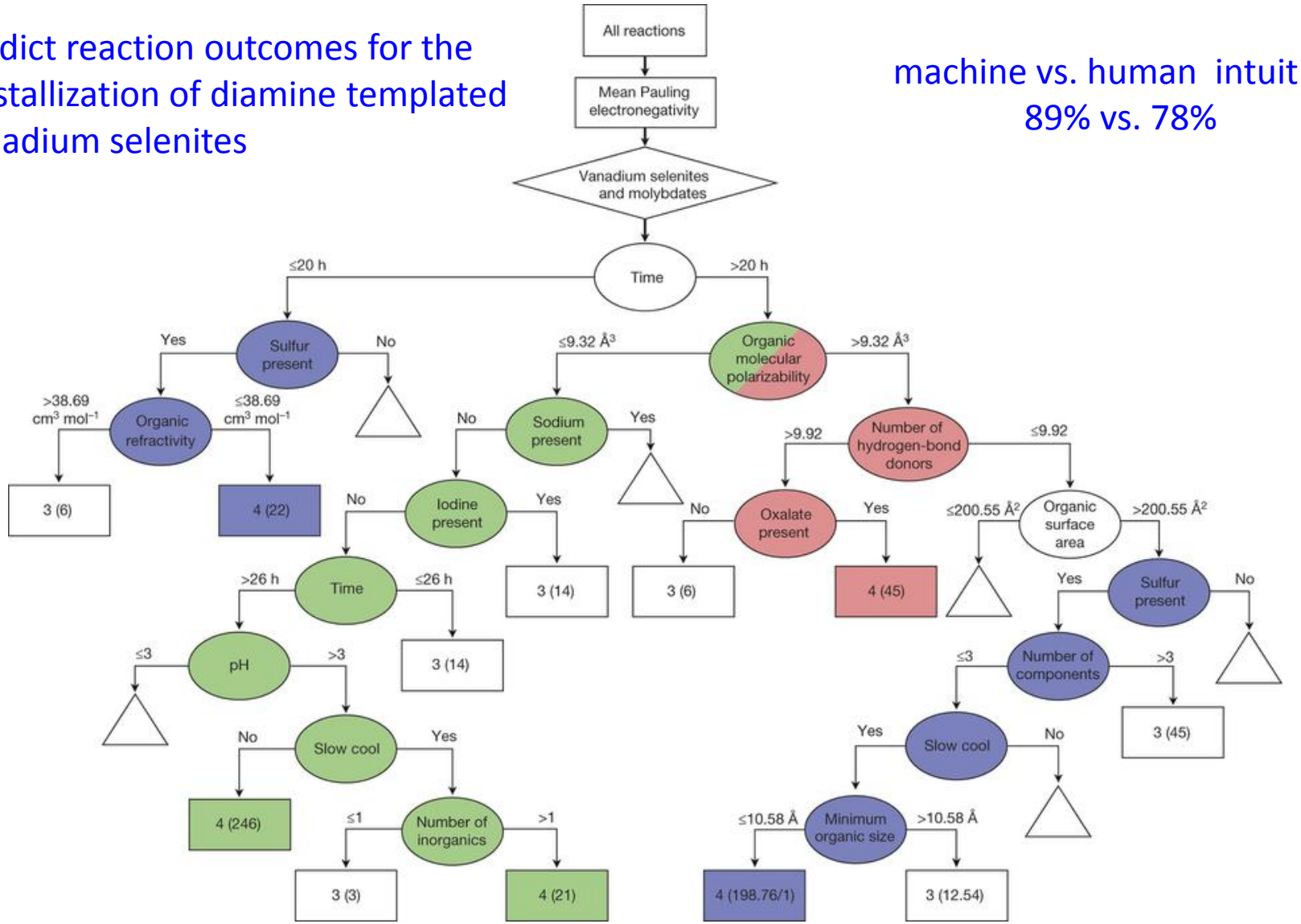


Martens, D., Baesens, B., Gestel, T.V., IEEE Transactions on Knowledge and Data Engineering, **2009**, 21(2): p. 178-191.

Rule-extraction approaches

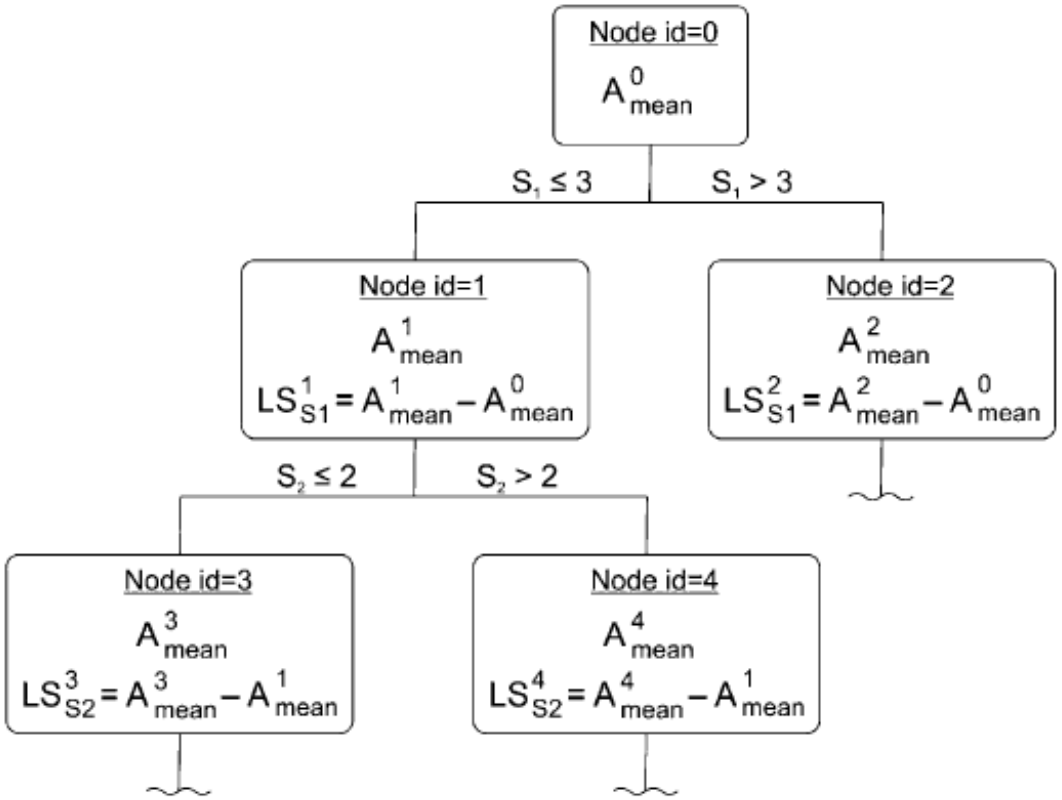
predict reaction outcomes for the crystallization of diamine templated vanadium selenites

machine vs. human intuition
89% vs. 78%



Raccuglia, P., Elbert, K.C., Adler, P.D.F., Falk, C., Wenny, M.B., Mollo, A., Zeller, M., Friedler, S.A., Schrier, J., Norquist, A.J., Nature, **2016**, 533(7601): p. 73-76.

Interpretation of random forest models



1) $$A_{mean} = \frac{1}{n} \sum_{i=1}^{n} A_i$$

2) $$LS_i^c = A_{mean}^c - A_{mean}^p$$

3) $$S_{k,i} = \frac{1}{T} \sum_{j=1}^{n} LS_{i,j}$$

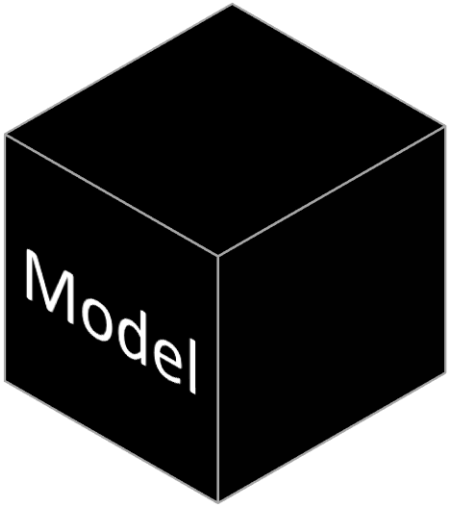
$S_{k,i}$ - contribution of i-th descriptor in k-th compound

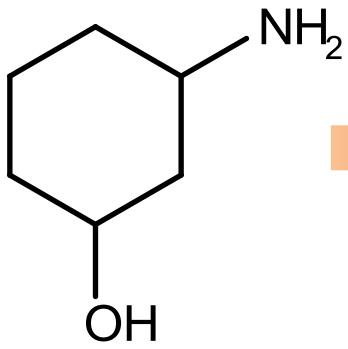
T - number of trees

$LS_{i,j}$ - local contribution of i-th descriptor where compound k fits the node

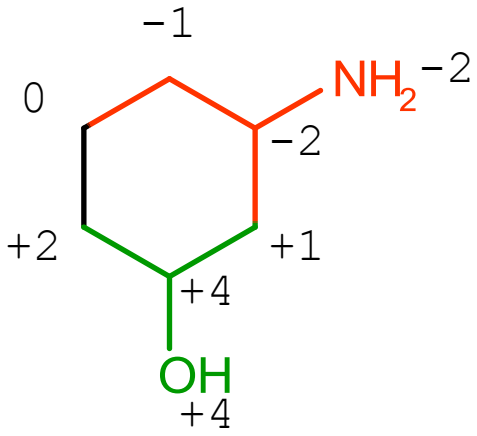
Kuz'min, V.E., Polishchuk, P.G., Artemenko, A.G., Andronati, S.A., Molecular Informatics, **2011**, 30: p. 593-603.

Visualization of descriptor contributions

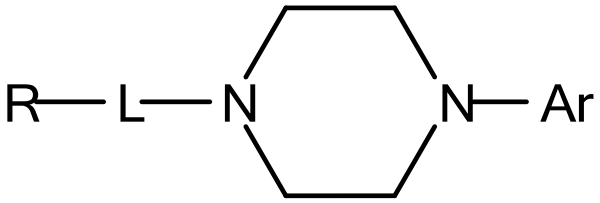




C–C–N –3
C–C–O +6

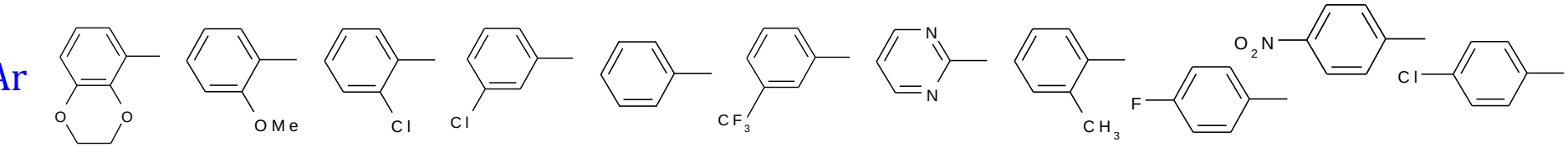


Interpretation of random forest models



347 agonists of 5-HT_{1A} receptor

Ar - substituted (hetero)aryls
L - polymethylene chain
R - various (poly)cyclic residues



PLS	0.84	0.18	0.03	-0.04	-0.06	-0.09	-0.11	-0.66	-0.73	-0.94	-0.96
RF	0.27	0.24	0.04	0.07	-0.02	0.11	0.04	-0.04	-0.55	-0.66	-0.66

L	$-(CH_2)_6-$	$-(CH_2)_5-$	$-(CH_2)_4-$	$-(CH_2)_3-$	$-(CH_2)_2-$	$-CH_2-$
PLS	0.8	0.71	0.81	0.08	-0.04	0.06
RF	0.14	0.19	0.14	-0.01	-0.03	0.05

Kuz'min, V.E., Polishchuk, P.G., Artemenko, A.G., Andronati, S.A., Molecular Informatics, **2011**, 30: p. 593-603.

Message

There are a lot of approaches which can be applied for interpretation of specific models

Interpretation results converge regardless machine learning method and interpretation approach used

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Variable importance

Gives information about relative importance of descriptors used for model building but not about the direction of their influence (positive or negative)

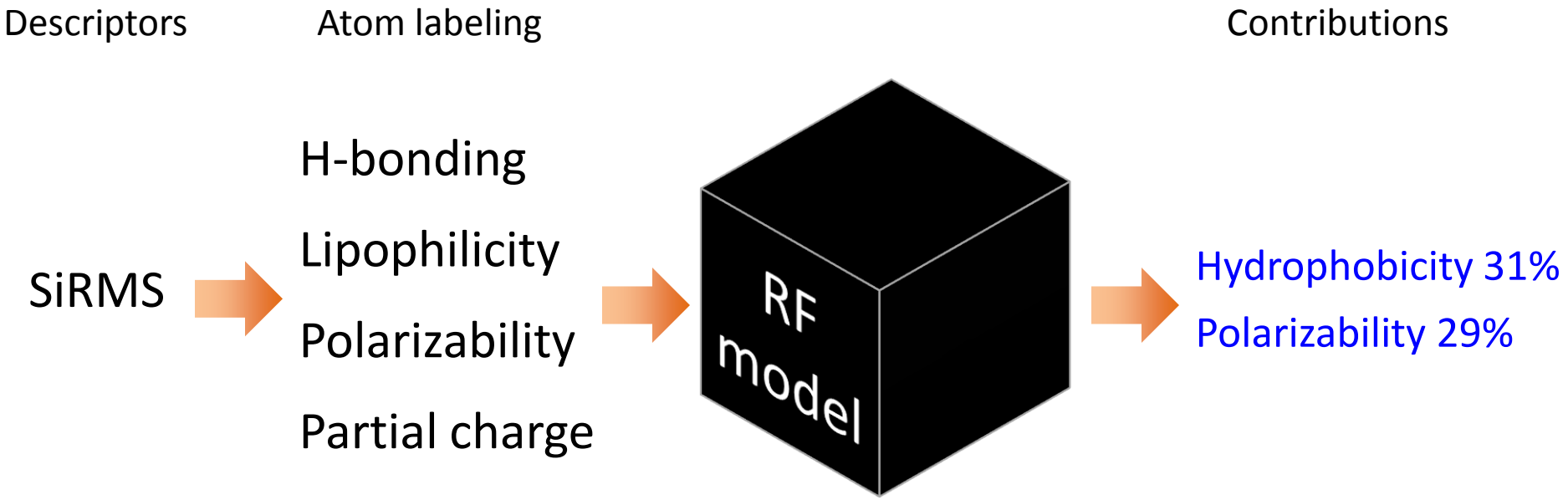
- add noise to input variables (descriptors)[1]
- permute variable values[2]

The more prediction accuracy is dropped the more important variable is.

[1] Györgyi, G., Physical Review Letters, **1990**, 64(24): p. 2957-2960.
[2] Breiman, L., Machine Learning, **2001**, 45(1): p. 5-32.

Variable importance

toxicity on *Tetrahymena Pyriformis*

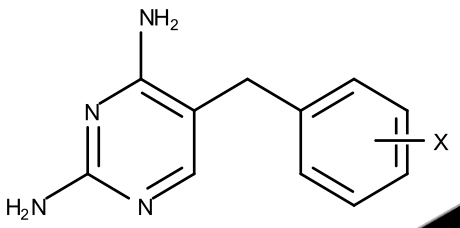


Polishchuk, P.G., Muratov, E.N., Artemenko, A.G., Kolumbin, O.G., Muratov, N.N., Kuz'min, V.E., Journal of Chemical Information and Modeling, **2009**, 49(11): p. 2481-2488.

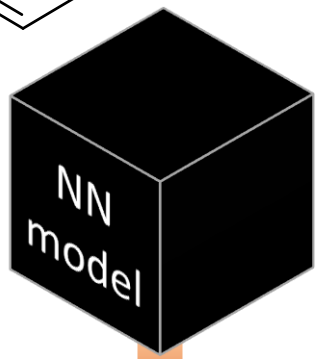
Sensitivity analysis

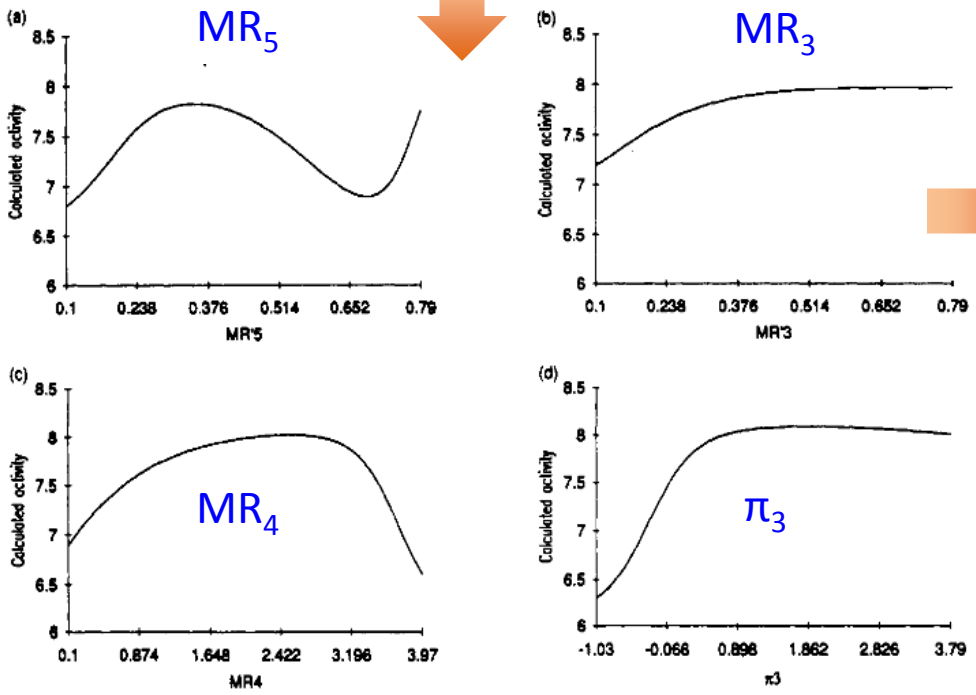
Explores the dependence of output values to systematic changes in descriptor values while values of all other descriptors remain constant

Sensitivity analysis



inhibitors of dihydrofolate reductase
(substituents X are at 3, 4, and 5 positions)





linear model

	previous	updated
MR_5^3		11.79
MR_5^2		15.74
MR_5	0.95	6.55
MR_3	0.89	0.89
MR_4	0.80	0.80
MR_4^2	-0.21	-0.21
π_3	1.58	1.58
$Log(\beta*10^{\pi 3}+1)$	-1.77	-1.77
intercept	6.65	6.24
RMSE	0.093	0.074

So, S.S., Richards, W.G., Journal of Medicinal Chemistry, **1992**, 35(17): p. 3201-3207.

Partial derivatives

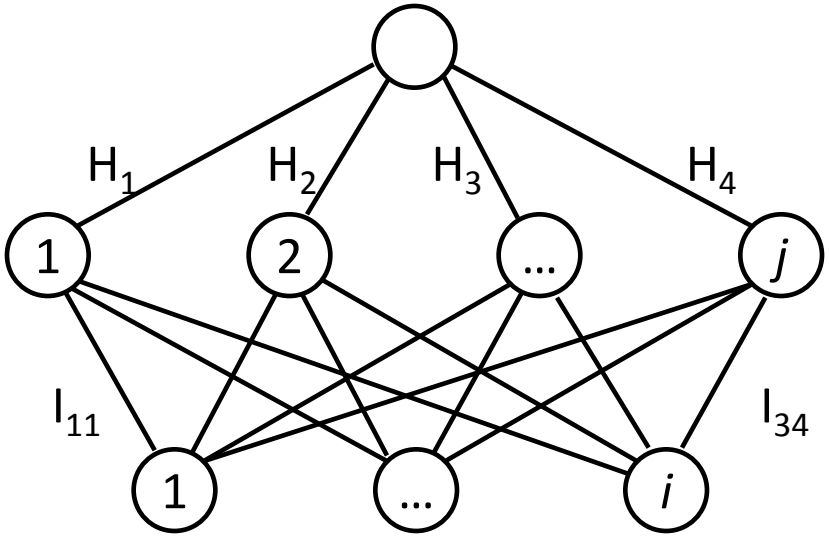
Partial derivatives (or local sensitivity analysis) estimates "regression coefficients" from nonlinear models for a particular data point (compounds) in a chemical space

$$f = ax + by + c$$

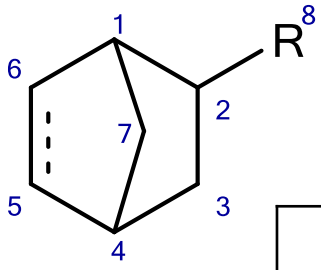
$$\frac{\partial f}{\partial x} = a$$

$$\frac{\partial f}{\partial y} = b$$

Partial derivatives



$$\frac{\partial Y}{\partial x_i} = \sum_j f'(y_j) I_{ij} g'(y) H_j$$



^{13}C NMR chemical shifts of exo and endo- nonbornanes and nonbornenes

(NN architecture 8-14-2)

	C_1	C_2	C_3	C_4	C_5	C_6	C_7
exo	-0.009	0.088	0.031	-0.111	-0.107	0.141	-0.213
endo	0.010	-0.088	-0.032	0.110	0.109	-0.141	0.214

Aoyama, T., Ichikawa, H., Journal of Chemical Information and Computer Sciences, **1992**, 32(5): p. 492-500.

Partial derivatives

Numerical solution

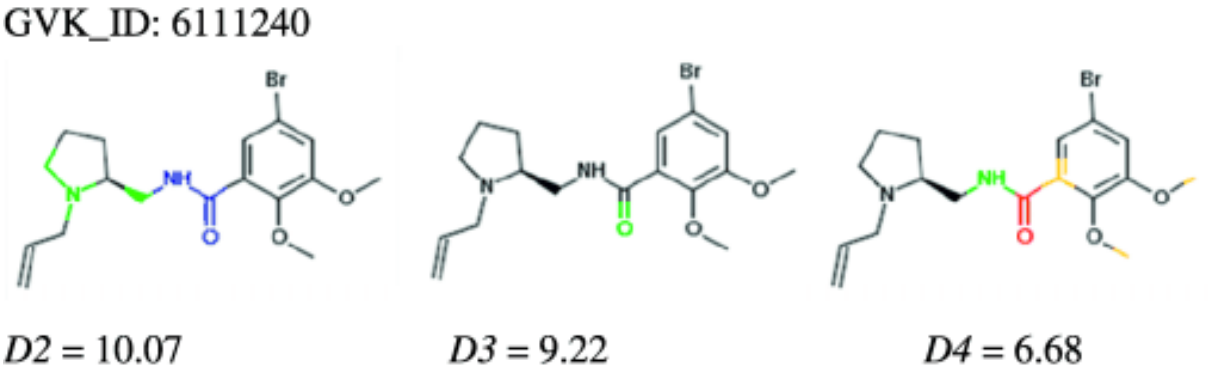
$$C = \frac{f(x + \delta) - f(x)}{\delta}$$ (forward difference)

$$C = \frac{f(x) - f(x - \delta)}{\delta}$$ (backward difference)

$$C = \frac{f(x + \delta/2) - f(x - \delta/2)}{\delta}$$ (central difference)

Dopamine inhibitors

SVM models on ECFP



Hasegawa, K., Keiya, M., Funatsu, K., Molecular Informatics, **2010**, 29(11): p. 793-800.

Partial derivatives

+ regression/classification
+ linear, non-linear, consensus
- k-NN models
- proper estimation of differentiation error

“model → descriptor → (structure)” paradigm

All models regardless machine learning method used are interpretable

Limitation:

use of only interpretable descriptors

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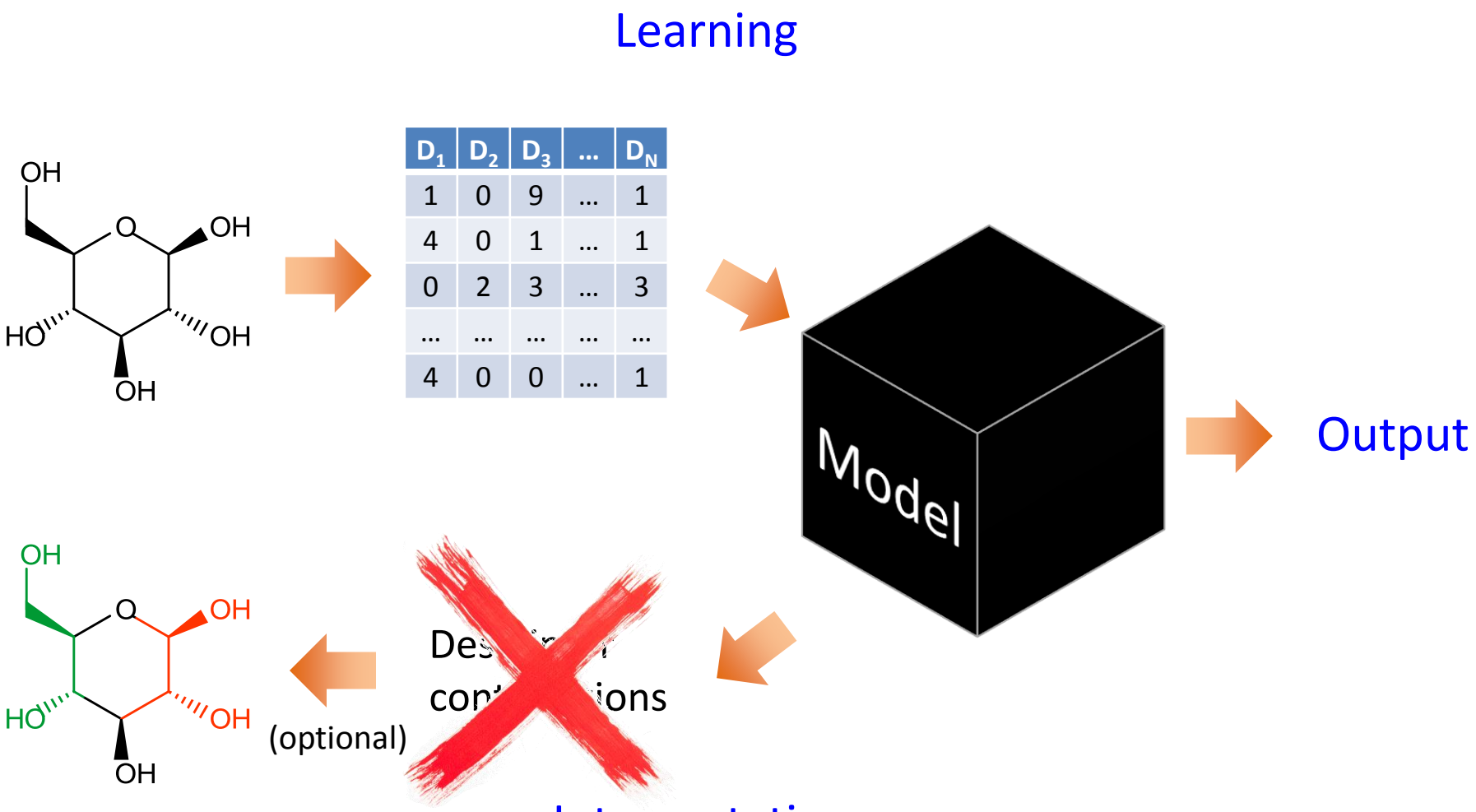
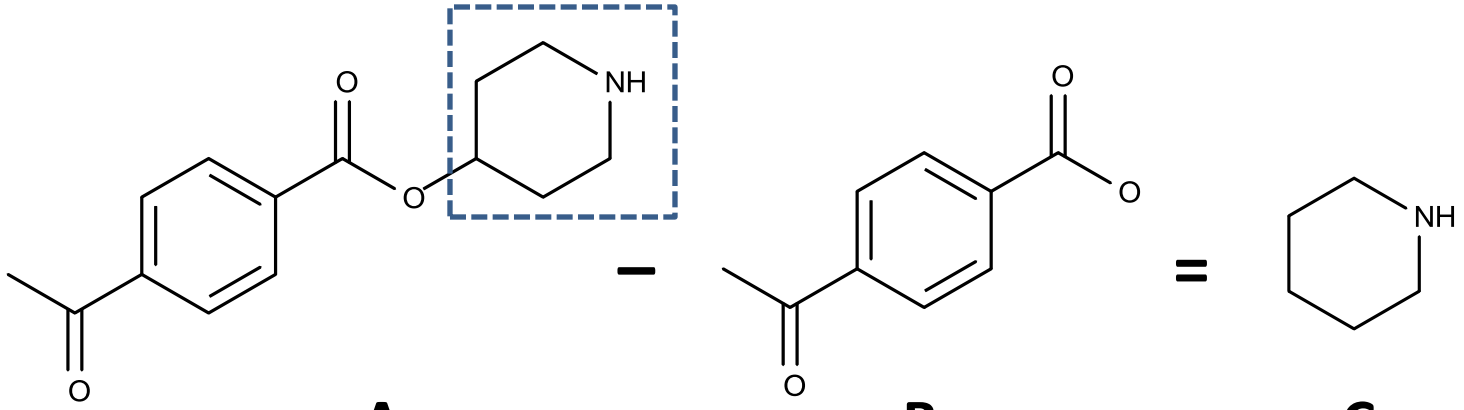
Learning and interpretation



“model → structure” paradigm

Universal structural interpretation of QSAR models



$Activity_{pred}(A)$	$Activity_{pred}(B)$	Contribution(C)
$f(A) = x$	$f(B) = y$	$W(C) = x - y$

Polishchuk, P. G.; Kuz'min, V. E.; Artemenko, A. G.; Muratov, E. N.
Molecular Informatics **2013,** *32*, 843-853

“Model → structure” interpretation approaches

1. Similarity maps

Riniker, S.; Landrum, G. Similarity maps - a visualization strategy for molecular fingerprints and machine-learning methods. *Journal of Cheminformatics* **2013,** *5*, 43

2. Universal structural interpretation

Polishchuk, P. G.; Kuz'min, V. E.; Artemenko, A. G.; Muratov, E. N. Universal Approach for Structural Interpretation of QSAR/QSPR Models. *Molecular Informatics* **2013,** *32*, 843-853

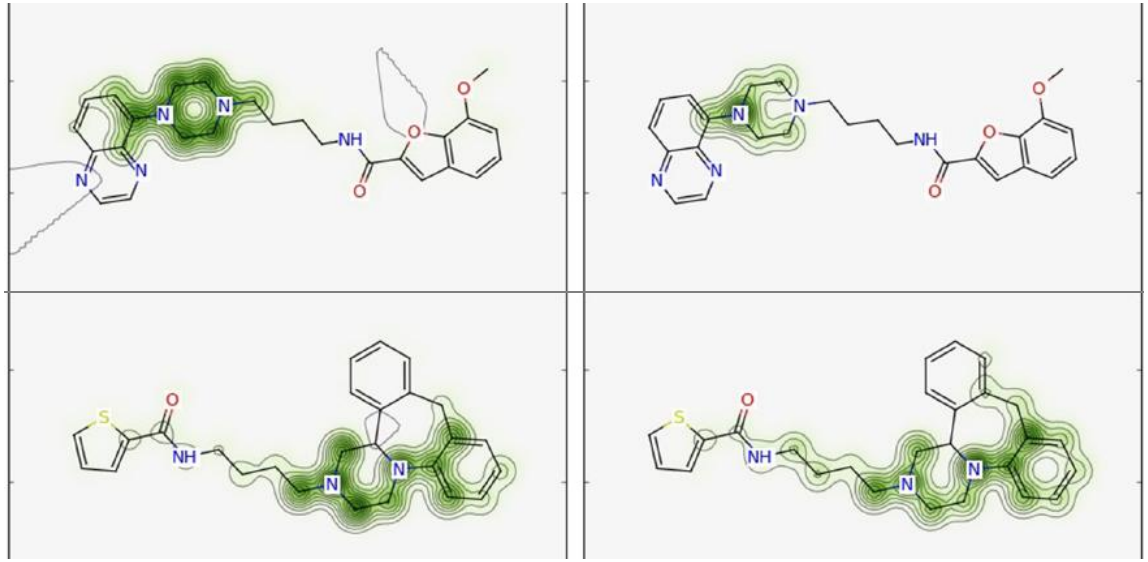
3. Computational matched molecular pairs

Sushko, Y.; Novotarskyi, S.; Korner, R.; Vogt, J.; Abdelaziz, A.; Tetko, I. Prediction-driven matched molecular pairs to interpret QSARs and aid the molecular optimization process. *Journal of Cheminformatics* **2014,** *6*, 48

Similarity maps (per atom interpretation)

Dopamine D3 inhibitors

RF NB



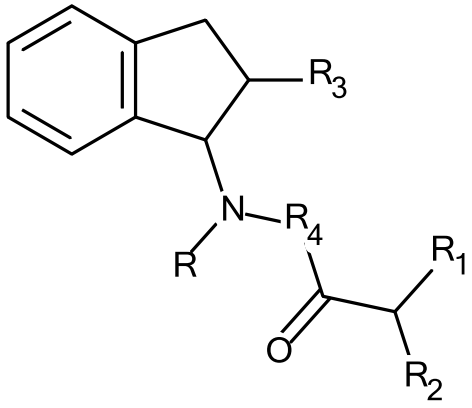
\+ implemented in RDKit (http://rdkit.org)

\- implementation supports only classification models built with atom pairs, topological torsions or Morgan fingerprints

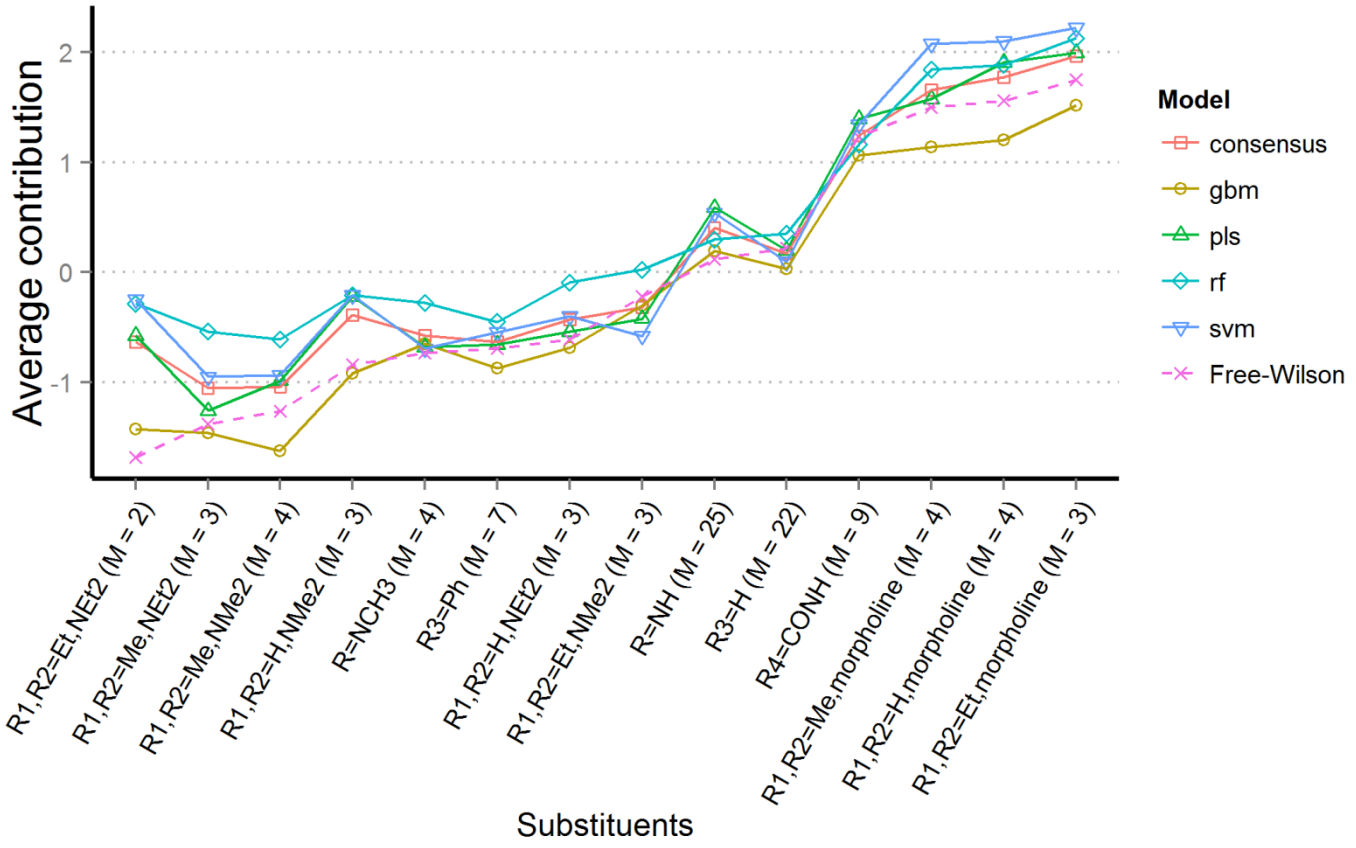
Riniker, S., Landrum, G., Journal of Cheminformatics, **2013**, 5(1): p. 43.

Universal structural interpretation vs. Free-Wilson

Comparison with Free-Wilson



R = H, CH_3;
R_1 = H, CH_3, C_2H_5;
R_2 = $N(CH_3)_2$,
$N(C_2H_5)_2$,
morpholino;
R_3 = H, phenyl;
R_4 = nothing, -CONH-

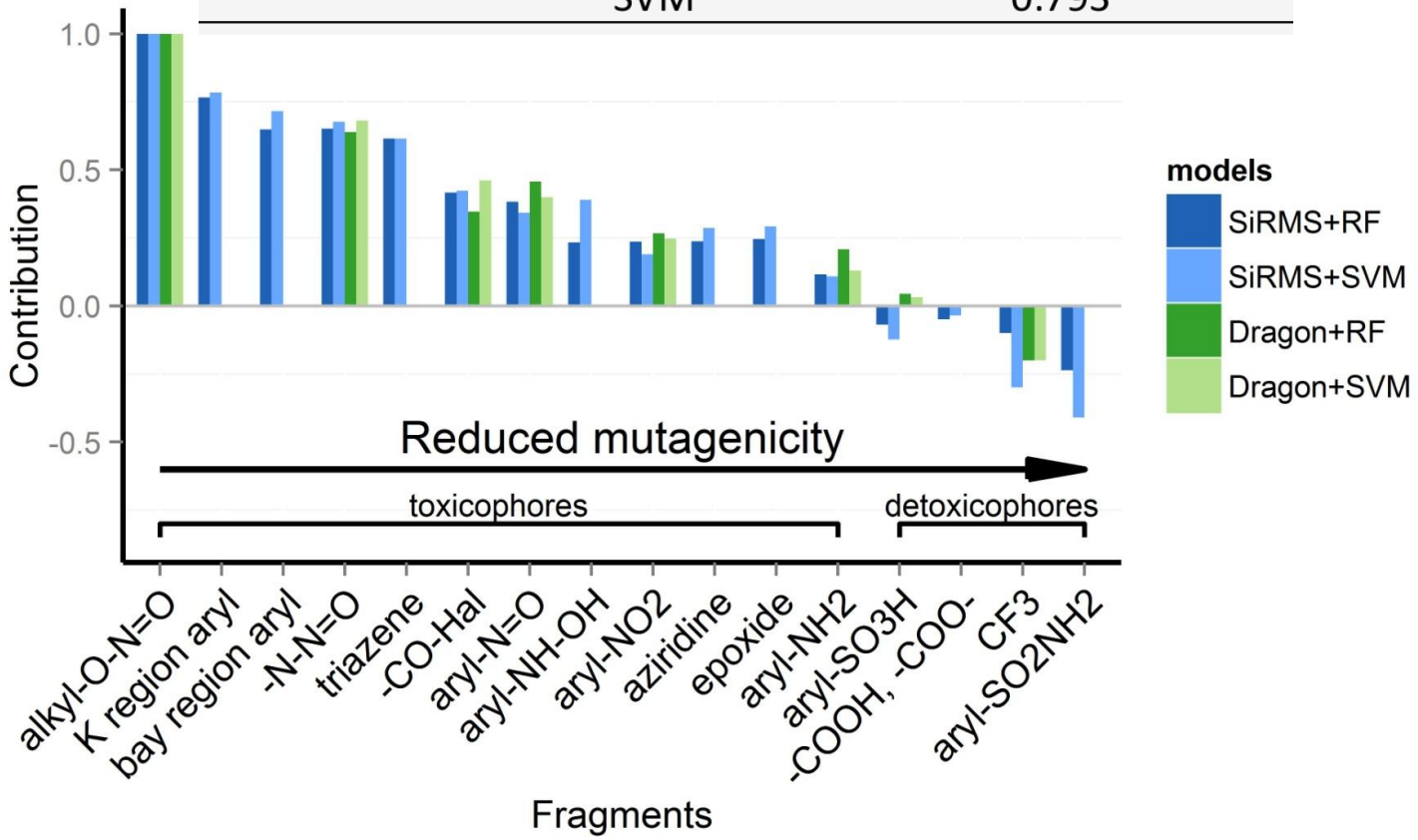


Polishchuk P, Tinkov O, Khristova T, Ognichenko L, Kosinskaya A, Varnek A, Kuz'min V. *Journal of Chemical Information and Modeling* **2016**, 56, 1455-1469.

Universal structural interpretation (Ames)

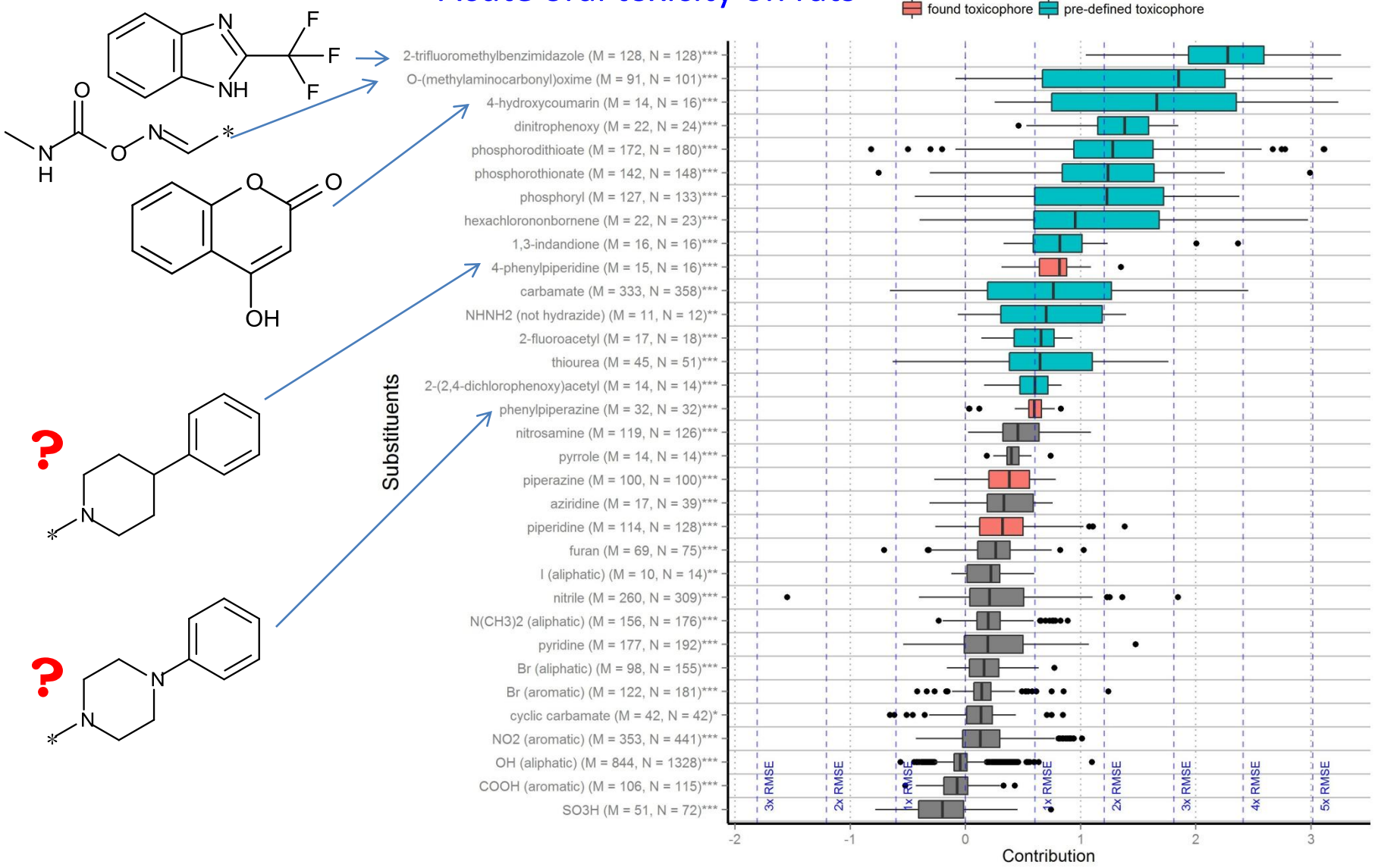
5-fold external cross validation results

Descriptors	Algorithm	Balanced Accuracy
SiRMS	RF	0.817
	SVM	0.800
Dragon	RF	0.816
	SVM	0.793



Polishchuk, P. G.; Kuz'min, V. E.; Artemenko, A. G.; Muratov, E. N.
Molecular Informatics **2013,** *32*, 843-853

Universal structural interpretation

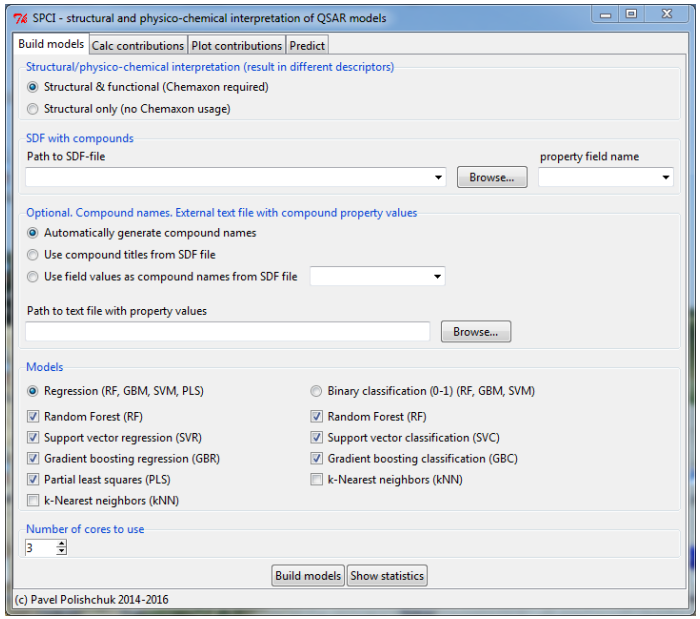


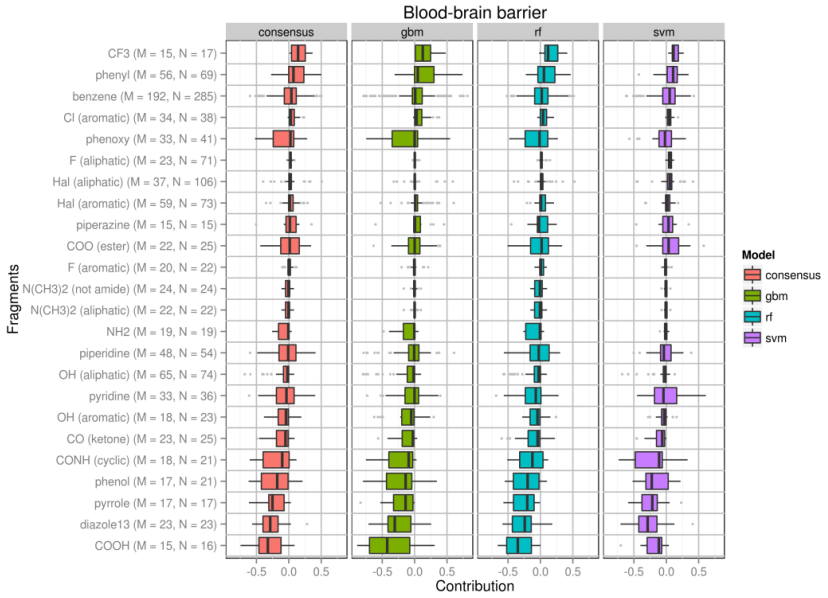
Polishchuk P, Tinkov O, Khristova T, Ognichenko L, Kosinskaya A, Varnek A, Kuz'min V. *Journal of Chemical Information and Modeling* **2016**, 56, 1455-1469.

Message

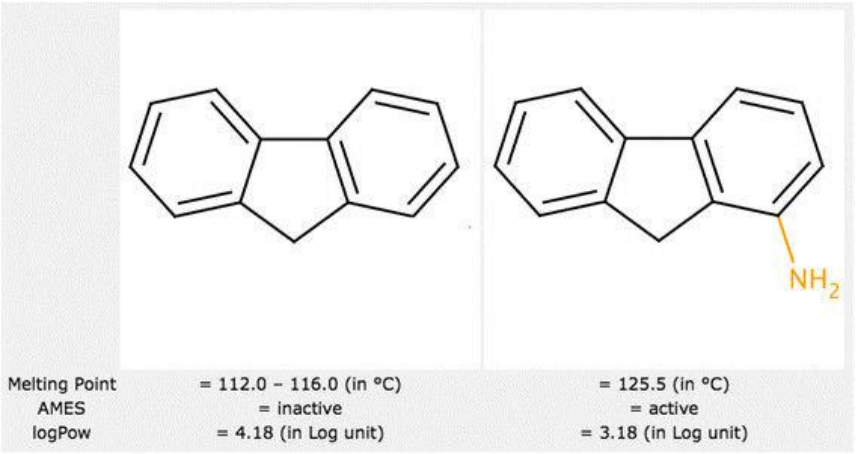
Interpretation results converge regardless machine learning method and descriptors used

Implemented in open-source SPCI software https://github.com/DrrDom/spci and R package https://github.com/DrrDom/rspci





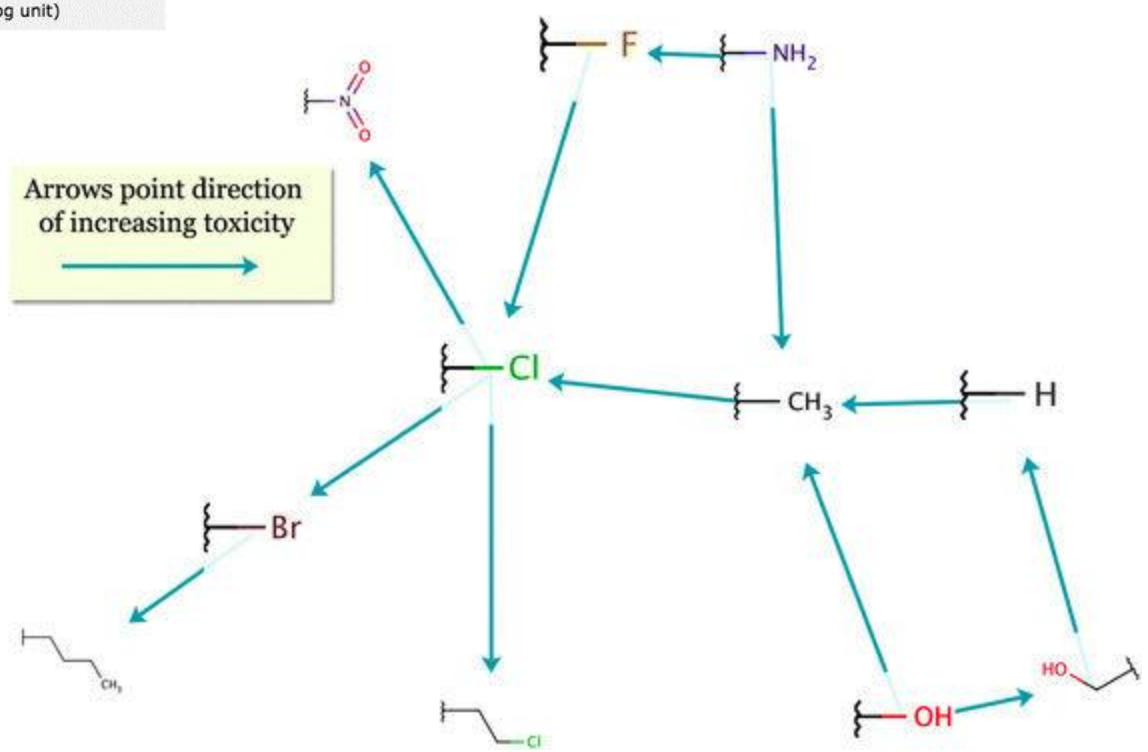
Prediction-driven MMP



MMP Example

f(A-B) - f(A-C) = W(B→C)

Aquatic toxicity



Sushko, Y., Novotarskyi, S., Korner, R., Vogt, J., Abdelaziz, A., Tetko, I. Journal of Cheminformatics, **2014**, 6(1): p. 48.

Message

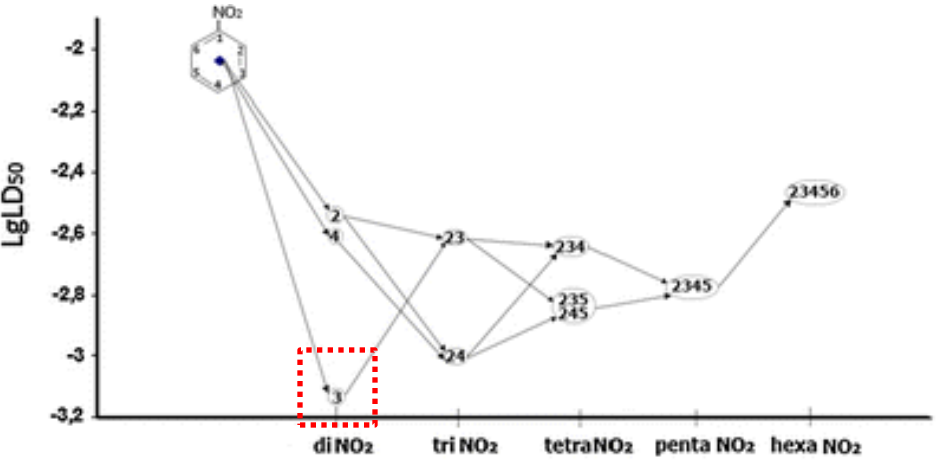
Prediction-driven MMP can improve coverage of chemical space (fill gaps)

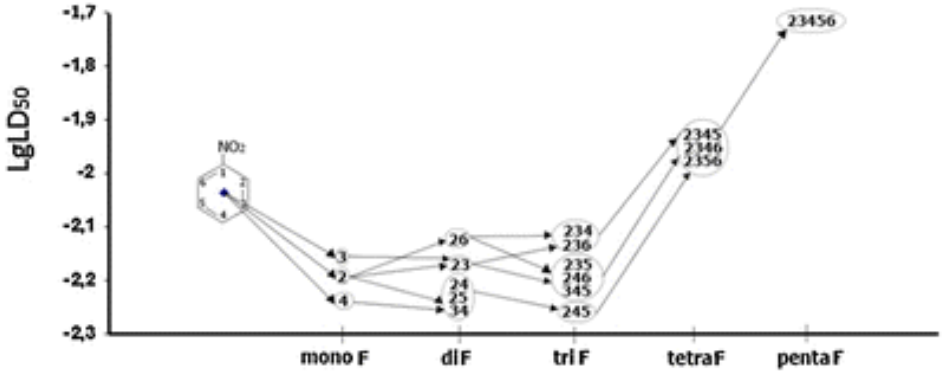
Ignores molecular context which can be important

Implemented on http://ochem.eu

Design of molecular series

acute toxicity on rats





1,3 dinitrobenzene has higher toxicity than 1,2- and 1,4-dinitrobenzes that may be a result of a different mechanism of action, e.g. it may act as uncoupler of oxidative phosphorylation like 2,4 dinitrophenol

Tinkov, O.V., Ognichenko, L.N., Kuz'min, V.E., Gorb, L.G., Kosinskaya, A.P., Muratov, N.N., Muratov, E.N., Hill, F.C., Leszczynski, J., Structural Chemistry, **2016**, 27(1): p. 191-198.

Outline

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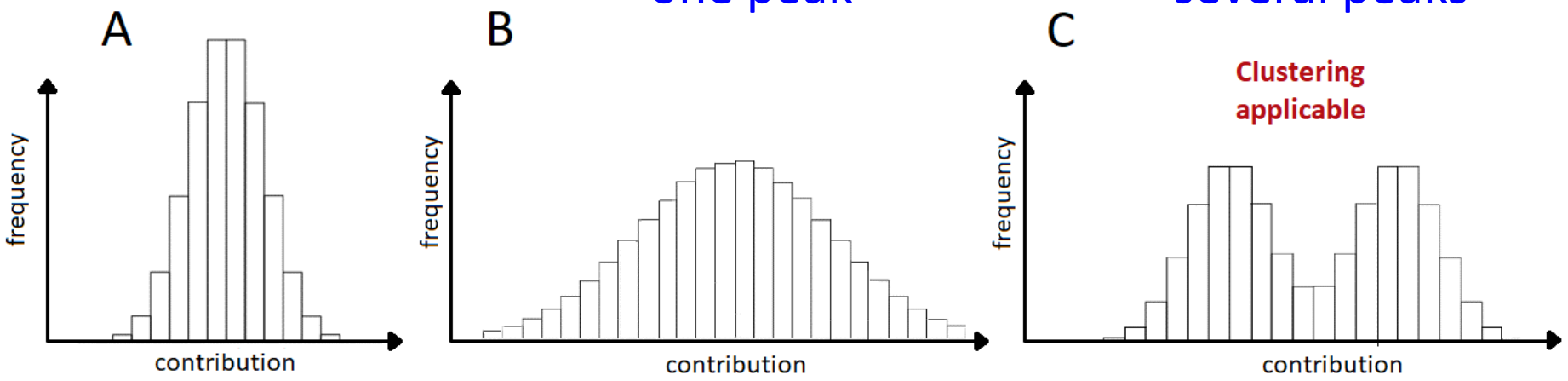
Analysis of context dependence of fragment contributions

Low variance

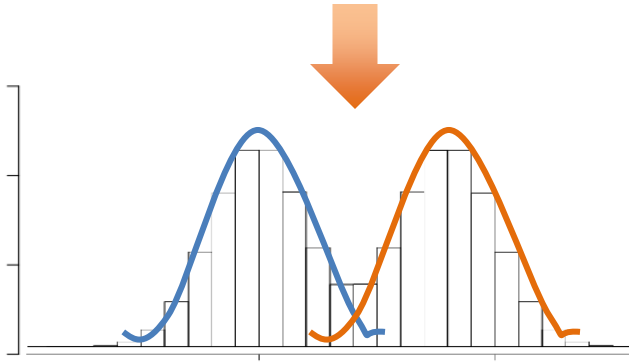
High variance

one peak

several peaks



Gaussian Mixture Model

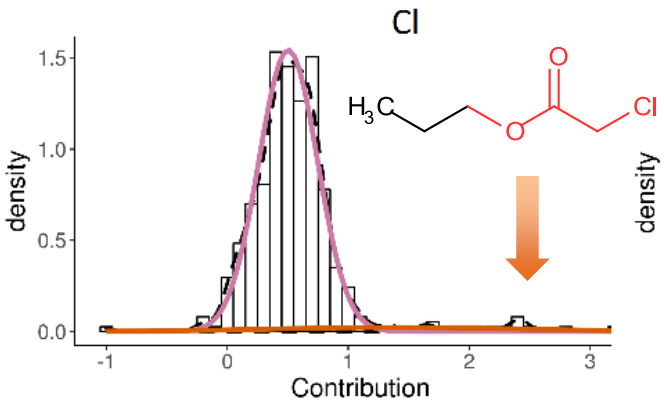


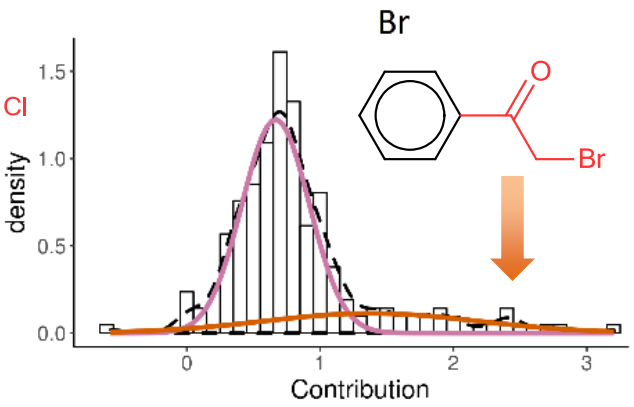
C(#N)[CX4][F,Cl,Br,I]

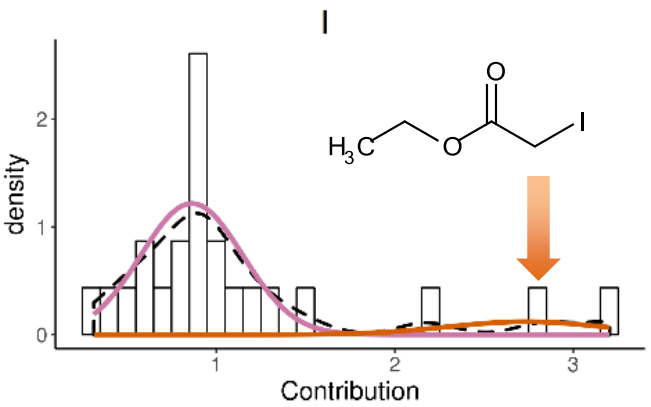
SMARTSminer

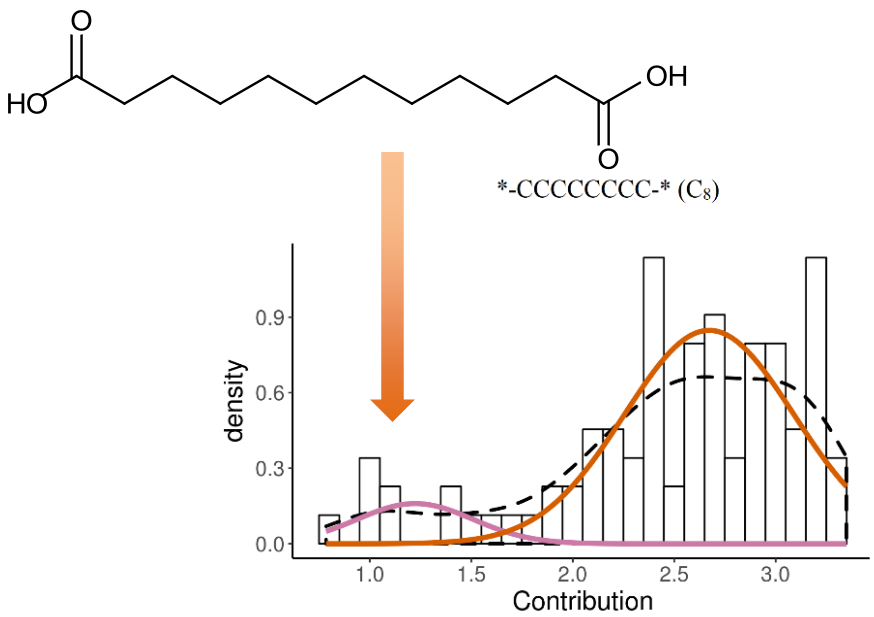
Analysis of context dependence of fragment contributions

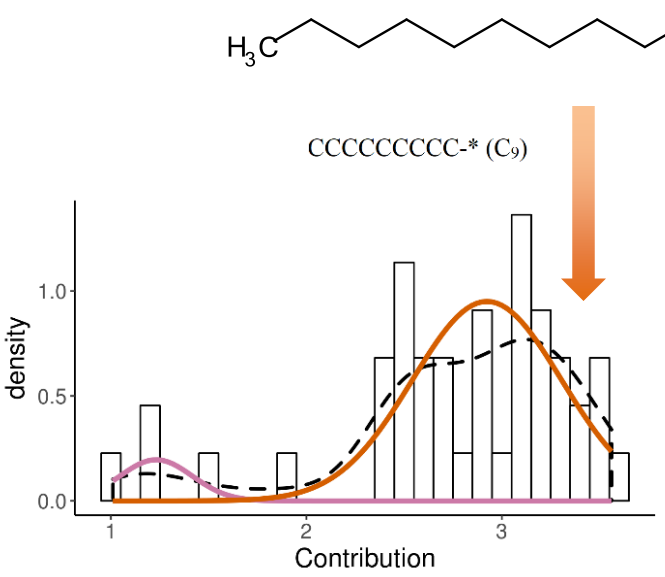
Toxicity on *Tetrahymena pyriformis*











unpublished results

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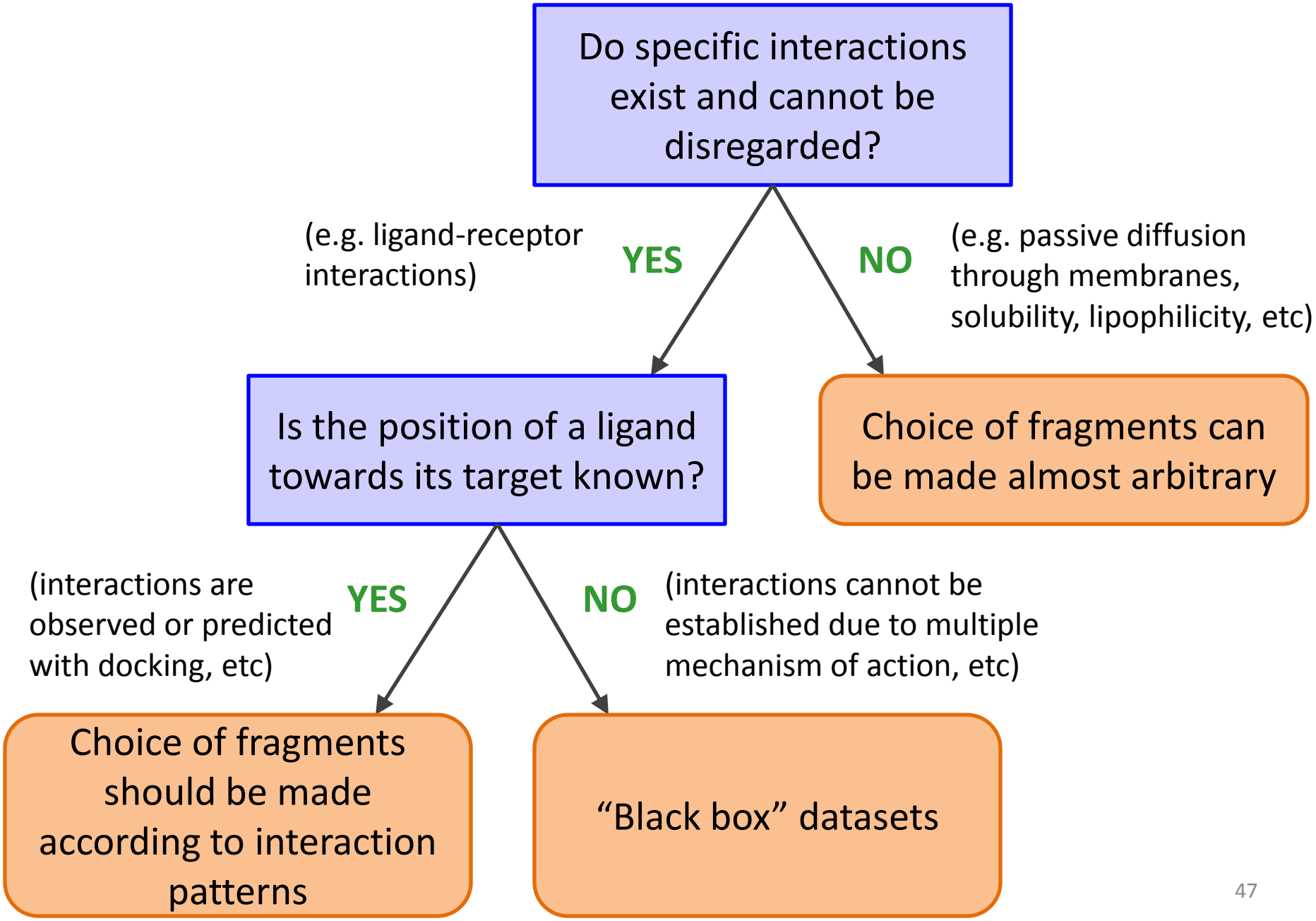
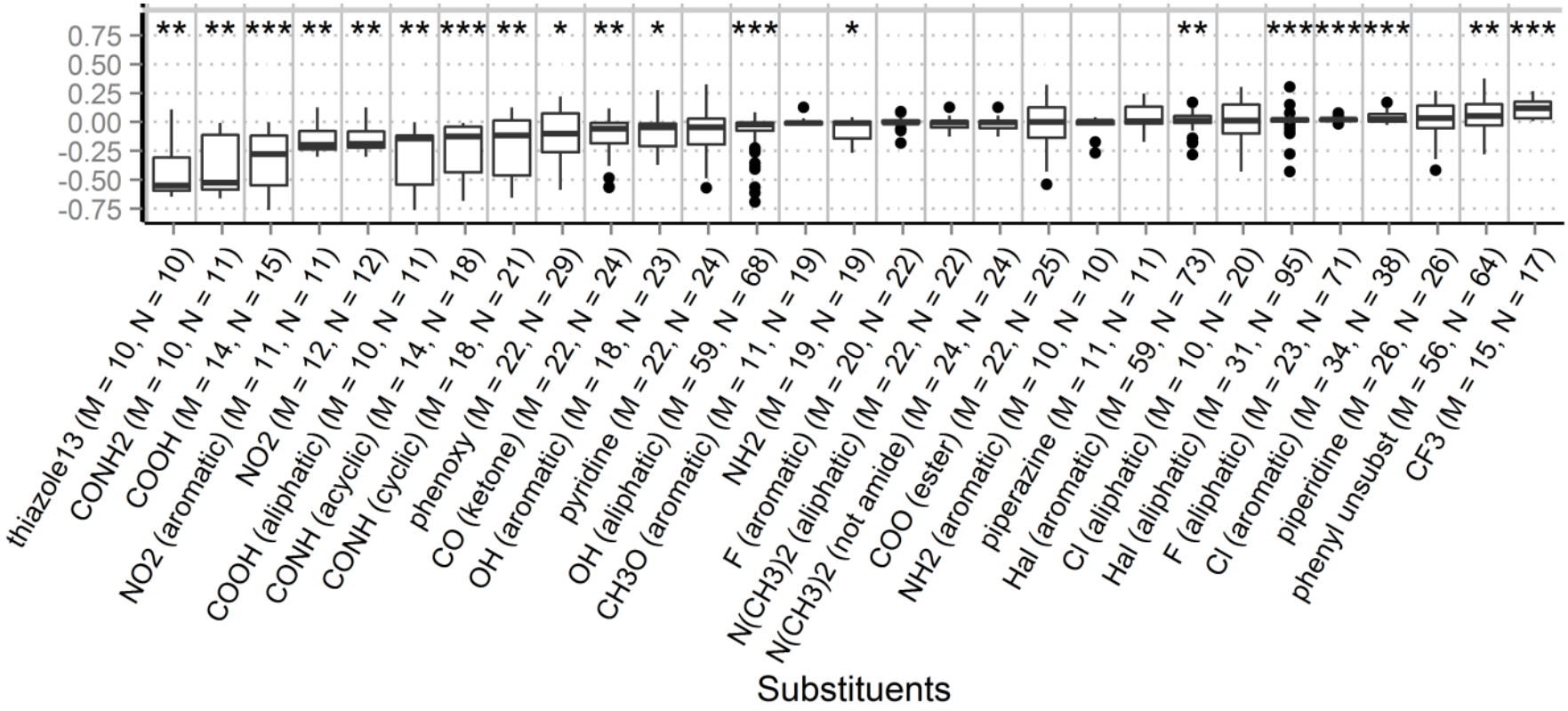
Structural interpretability of data sets (global interpretation)



Structural interpretability of data sets. Case 1

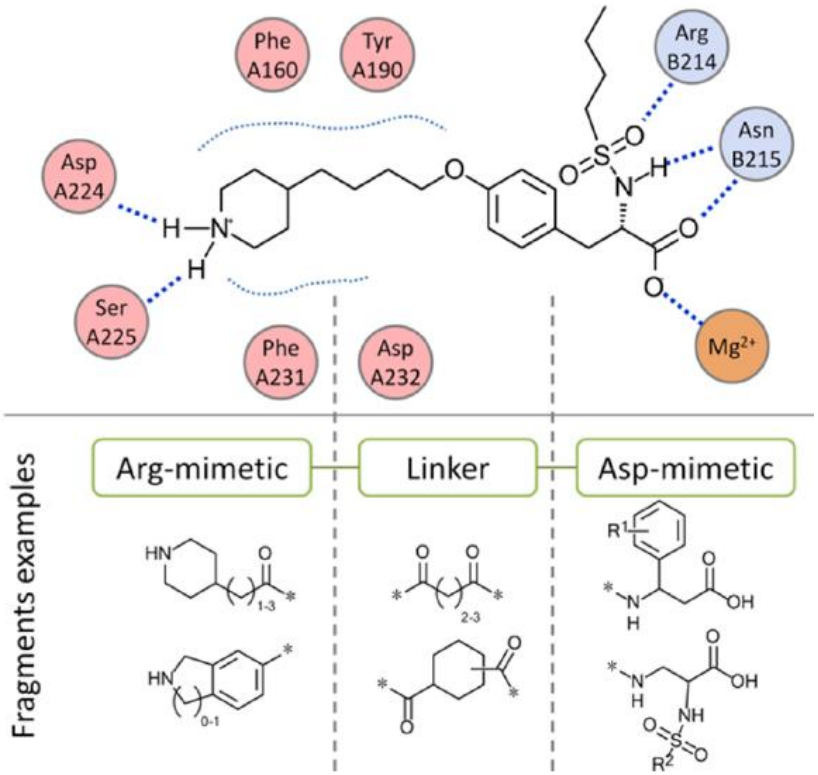
Blood-brain barrier permeability

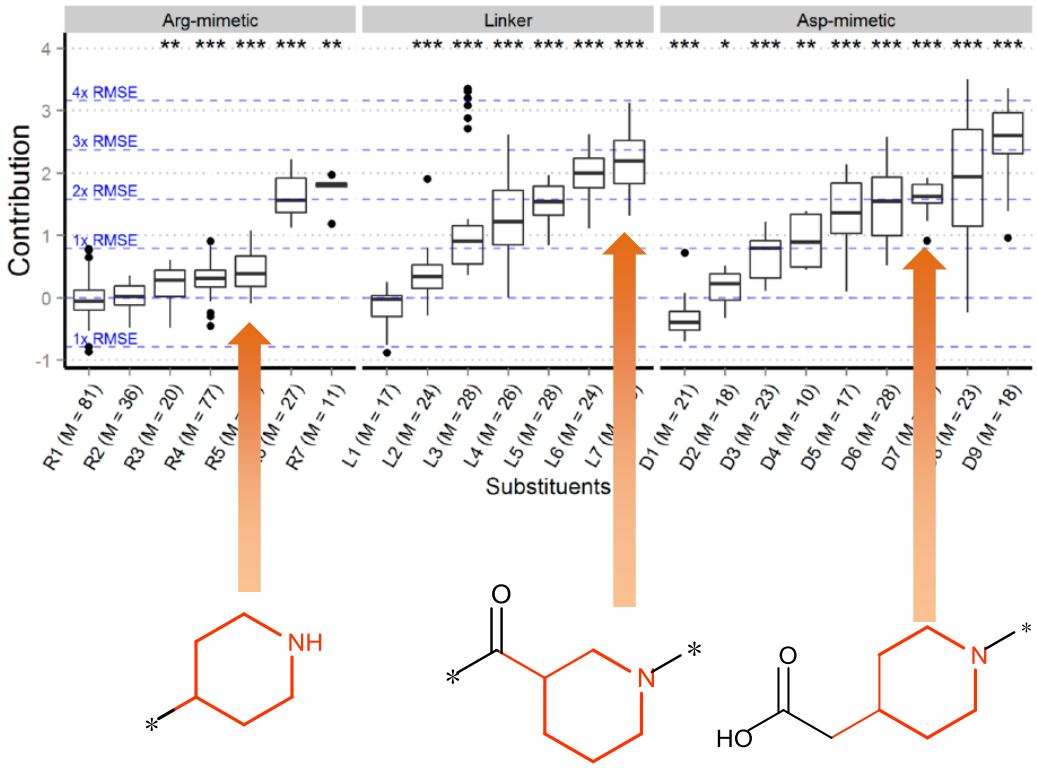


Polishchuk, P., Tinkov, O., Khristova, T., Ognichenko, L., Kosinskaya, A., Varnek, A., Kuz'min, V., Journal of Chemical Information and Modeling, **2016**, 56(8): p. 1455-1469.

Structural interpretability of data sets. Case 2

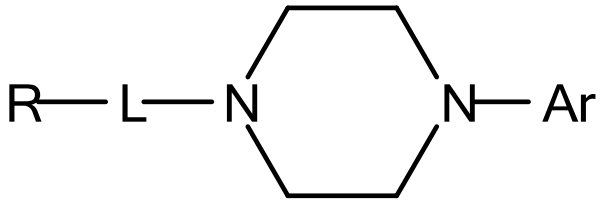
$\alpha_{IIb}\beta_3$ antagonists – RGD mimetics





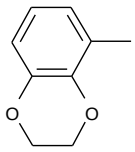
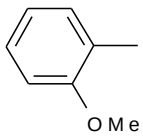
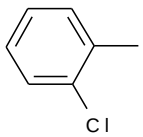
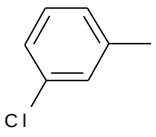
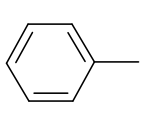
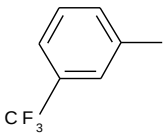
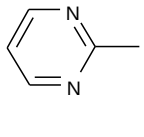
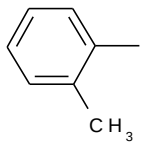
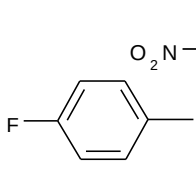
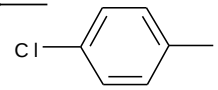
Polishchuk, P., Tinkov, O., Khristova, T., Ognichenko, L., Kosinskaya, A., Varnek, A., Kuz'min, V., Journal of Chemical Information and Modeling, **2016**, 56(8): p. 1455-1469.

Structural interpretability of data sets. Case 3



347 agonists of 5-HT_{1A} receptor

Ar - substituted (hetero)aryls
L - polymethylene chain
R - various (poly)cyclic residues

Ar											
PLS	0.84	0.18	0.03	-0.04	-0.06	-0.09	-0.11	-0.66	-0.73	-0.94	-0.96
RF	0.27	0.24	0.04	0.07	-0.02	0.11	0.04	-0.04	-0.55	-0.66	-0.66

L	$-(CH_2)_6-$	$-(CH_2)_5-$	$-(CH_2)_4-$	$-(CH_2)_3-$	$-(CH_2)_2-$	$-CH_2-$
PLS	0.8	0.71	0.81	0.08	-0.04	0.06
RF	0.14	0.19	0.14	-0.01	-0.03	0.05

Kuz'min, V.E., Polishchuk, P.G., Artemenko, A.G., Andronati, S.A., Molecular Informatics, **2011**, 30: p. 593-603.

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Applicability of interpretation approaches

<table>
<tr><th rowspan="2">Models</th><th colspan="2">Descriptors</th></tr>
<tr><th>interpretable</th><th>non-interpretable</th></tr>
<tr><td>linear regression</td><td>regression coefficients
(Hansch, Free-Wilson)</td><td rowspan="7">universal structural interpretation,
similarity maps,
computational matched molecular pairs and series</td></tr>
<tr><td>PLS (OPLS, O2PLS, etc)</td><td>regression coefficients,
X- and Y-scores,
variable importance</td></tr>
<tr><td>decision trees</td><td>logical rules</td></tr>
<tr><td>NN</td><td>variable importance based on weights and biases,
variable contributions</td></tr>
<tr><td>RF</td><td>variable importance based on permutation,
variable contributions</td></tr>
<tr><td>NN, SVM, RF</td><td>rule extraction</td></tr>
<tr><td>any model including consensus ones</td><td>partial derivatives,
variable importance based on permutation,
sensitivity analysis</td></tr>
<tr><td>Interpretation paradigm</td><td>model → descriptors → (structure)
or
model → structure</td><td>model → structure</td></tr>
</table>

Conclusion

Interpretation results of valid predictive models should converge independent of:

- interpretation approach
- descriptors
- machine learning method

All models are interpretable but not all end-points

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Perspective

Cite This: J. Chem. Inf. Model. 2017, 57, 2618-2639

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Interpretation of Quantitative Structure–Activity Relationship Models: Past, Present, and Future

Pavel Polishchuk*

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