HelmholtzZentrum münchen
German Research Center for Environmental Health

In Silico Prediction of ADMET properties with confidence: potential to speed-up drug discovery

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Layout of presentation

Introduction:

- Why accuracy of prediction is important?

Methods:

- What is a Distance to Model? How can we estimate it? What is a property-based space?

Case study 1: Prediction of environmental toxicity

Case study 2: Benchmarking of lipophilicity (logP) predictions

Case study 3: AMES test prediction

Case study 4: CYP450 prediction

Conclusions

Which common challenges do they face?

"One can not embrace the unembraceable."

Possible: 10^{60} - 10^{100} molecules theoretically exist

Achievable: 10^{20} - 10^{24} can be synthesized now
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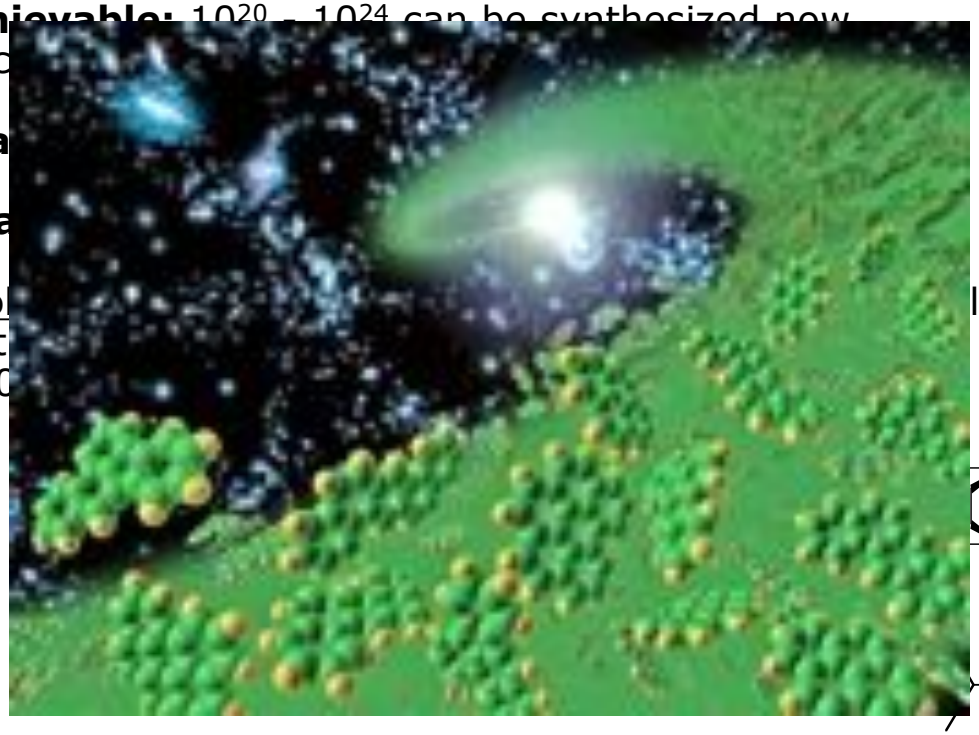
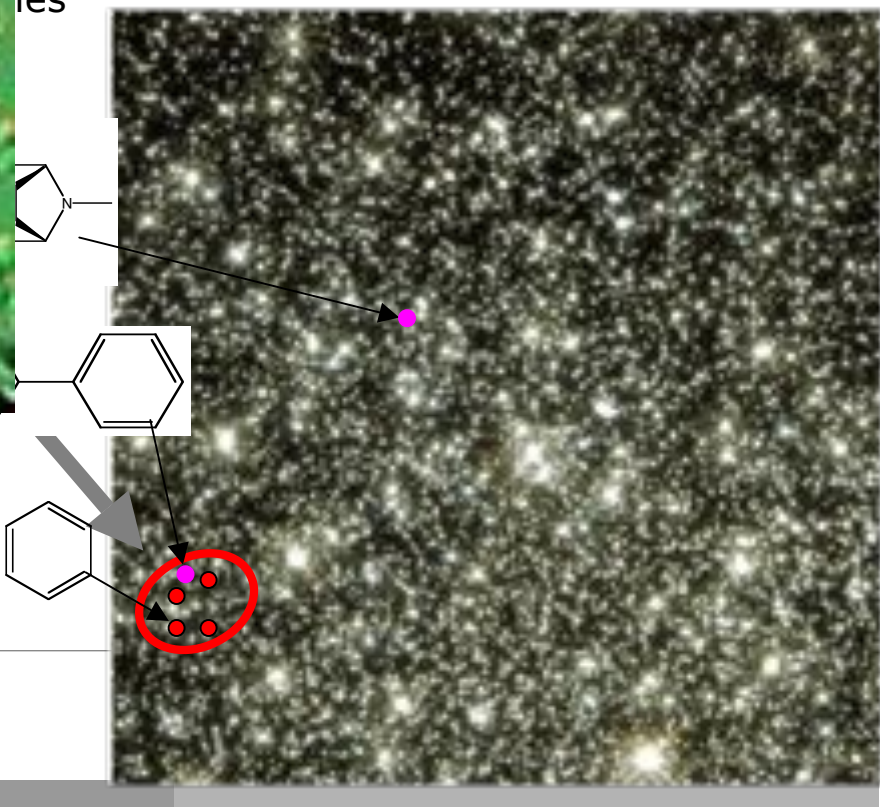


10^{80} atoms in the universe

Kozma Prutkov



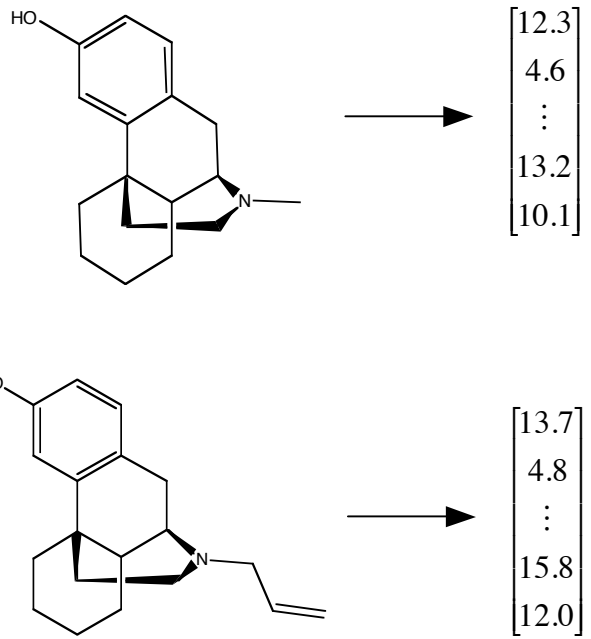
There is a need for methods which can estimate the accuracy of predictions!

Representation of Molecules

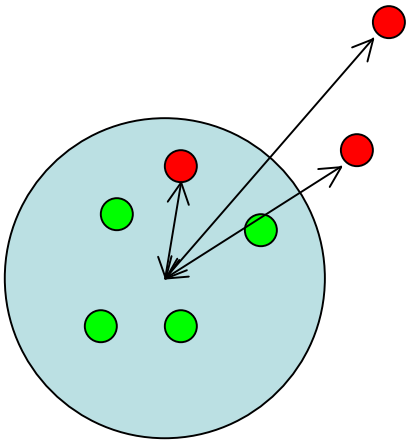
Can be defined with calculated properties (logP, quantum-chemical parameters, etc.)

Can be defined with a set of structural descriptors (toxicophores, 2D, 3D, etc).

The descriptors are used to define the applicability domain.



Distance to model:

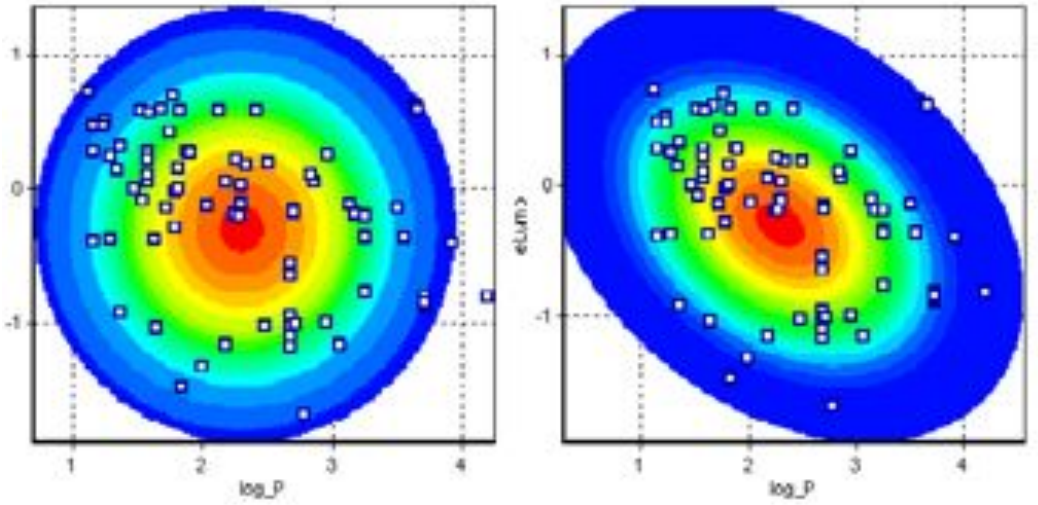


Examples of distances to models (DM) in descriptor space

1) Only two descriptors are used.

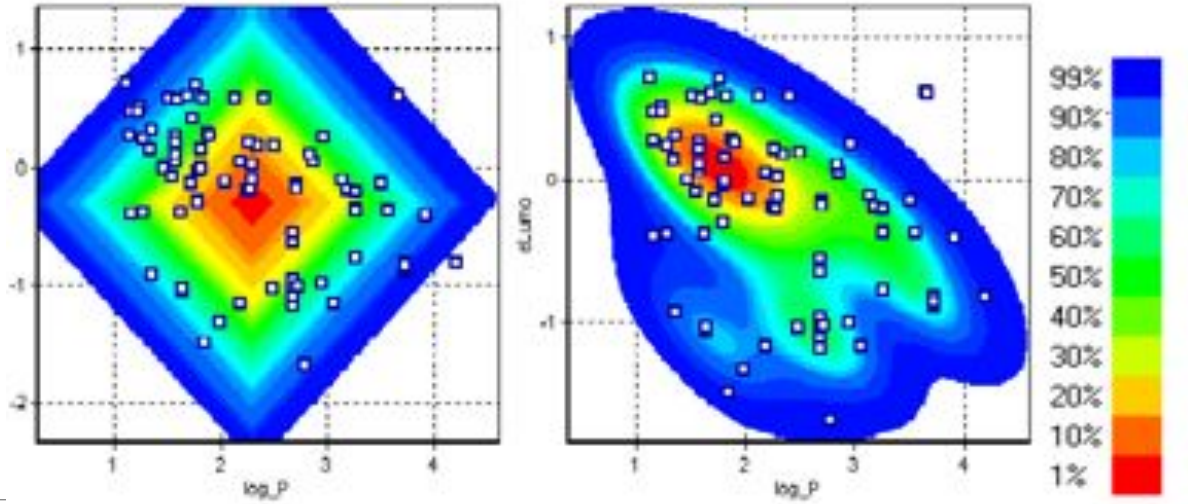
2) Colors refer to the same values.

3) More complex DMs (property-based DMs) also include the target property.[2]



Euclidian

Mahalanobis (Leverage)

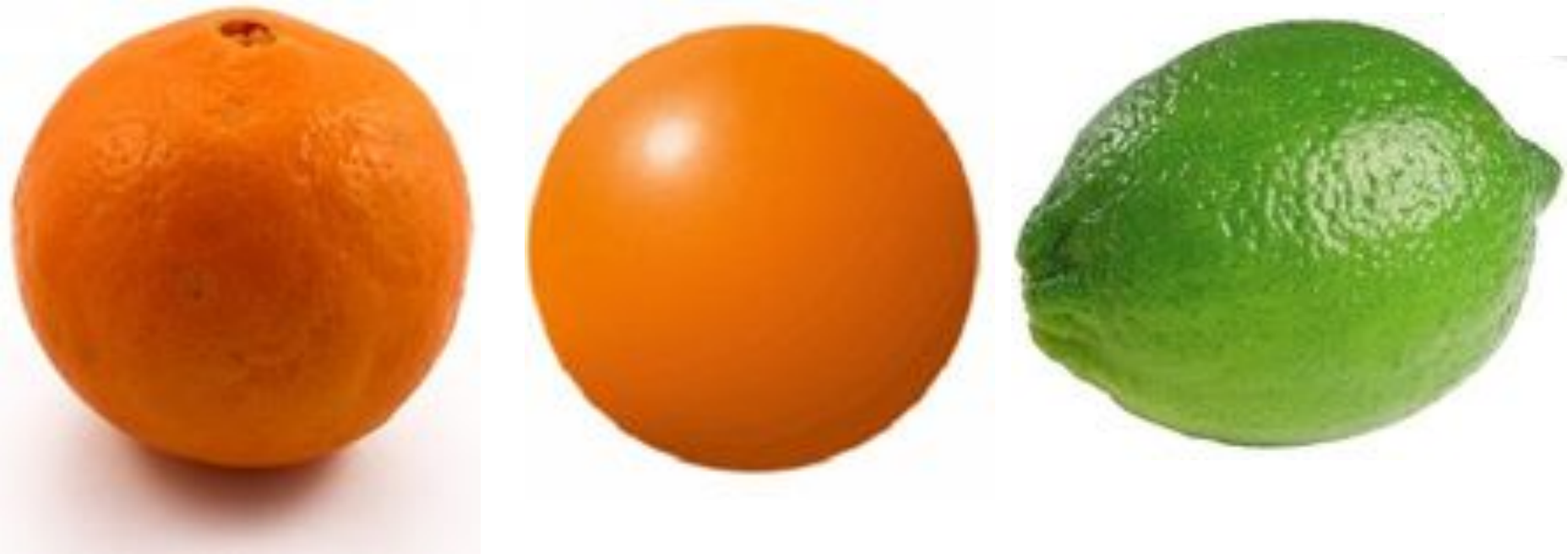


City-block

Probability-density

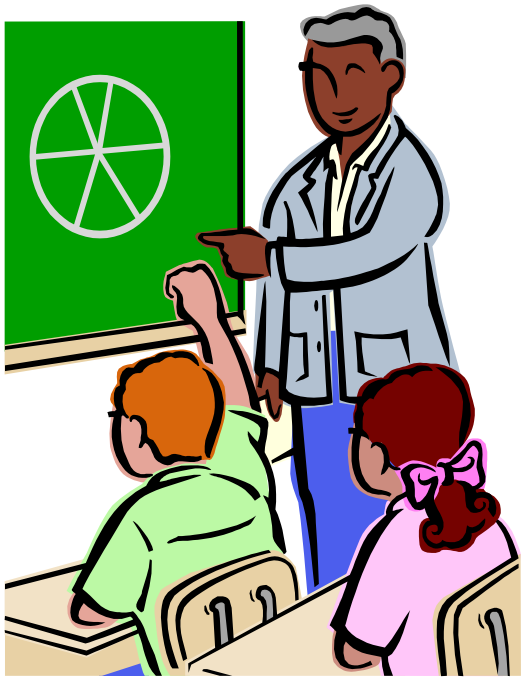
Jaworska et al, *ATLA*, **2005**, *33*, 445-459.
Tetko et al, *DDT*, **2006**, *11*, *700-7*.

The descriptor space challenge



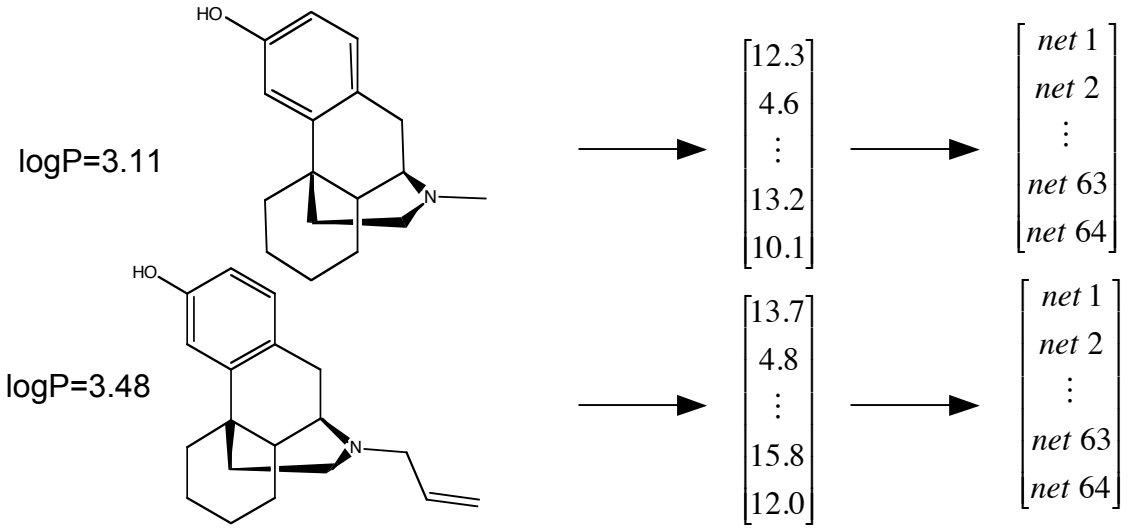
We need to know the target property and select correct descriptors!

Property-based space illustration



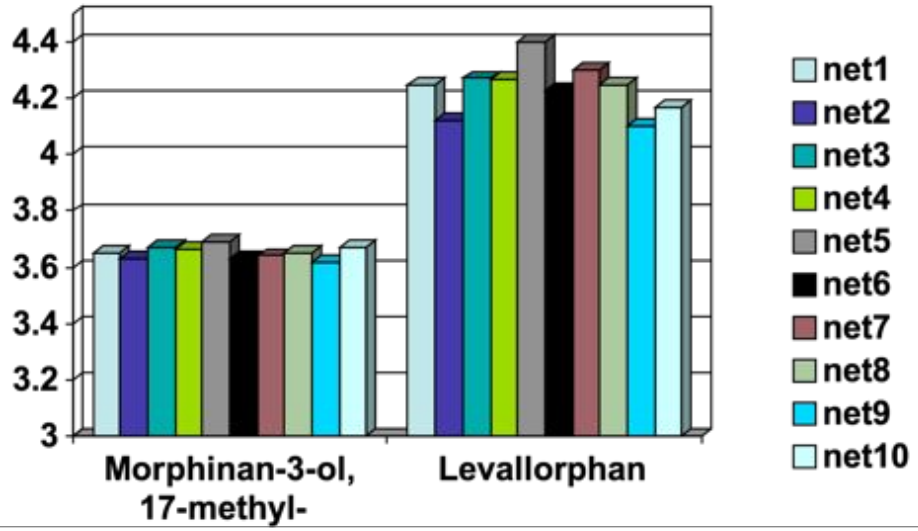
*Do they agree in their votes (**STD**)?*
*Do they have the same pattern of votes (**CORREL**)?*

Associative Neural Network Property-Based DMs



Morphinan-3-ol, 17-methyl-

Levallorphan



STD - standard deviation of ensemble predictions

CORREL - correlation between vectors of predictions

1: Estimation of toxicity against *T. pyriformis*

T. pyriformis

Prof. T.W. Schultz

The overall goal is to predict and to assess the reliability of predictions toxicity against T. pyriformis for chemicals directly from their structure.

Dataset: 1093 molecules

Zhu et al, *J. Chem. Inf. Model*, **2008,** *48*, 766-84.

CAse studies on the development and application of in-silico techniques for environmental hazard and risk assessment

Challenge (deadline was Sep. 10) co-organized with the European Neural Network Society

Analyzed QSARs (Quantitative Structure Activity Relationship) and distances to models (DM)

country	modeling techniques	descriptors	abbreviation	distances to models (in space)	
				descriptors	property-based
	ensemble of 192 kNN models	MolconnZ	kNN-MZ	EUCLID	STD
	ensemble of 542 kNN models	Dragon	kNN-DR	EUCLID	STD
	SVM	MolconnZ	SVM-MZ		
	SVM	Dragon	SVM-DR		
	SVM	Fragments	SVM-FR		
	kNN	Fragments	kNN-FR	EUCLID, TANIMOTO	
	MLR	Fragments	MLR-FR		
	MLR	Molec. properties (CODESSA-Pro)	MLR-COD		
	OLS	Dragon	OLS-DR	LEVERAGE	
	PLS	Dragon	PLS-DR	LEVERAGE	PLSEU
	ensemble of 100 neural networks	E-state indices	ASNN-ESTATE		CORREL, STD
All	consensus model	-	CONS		STD

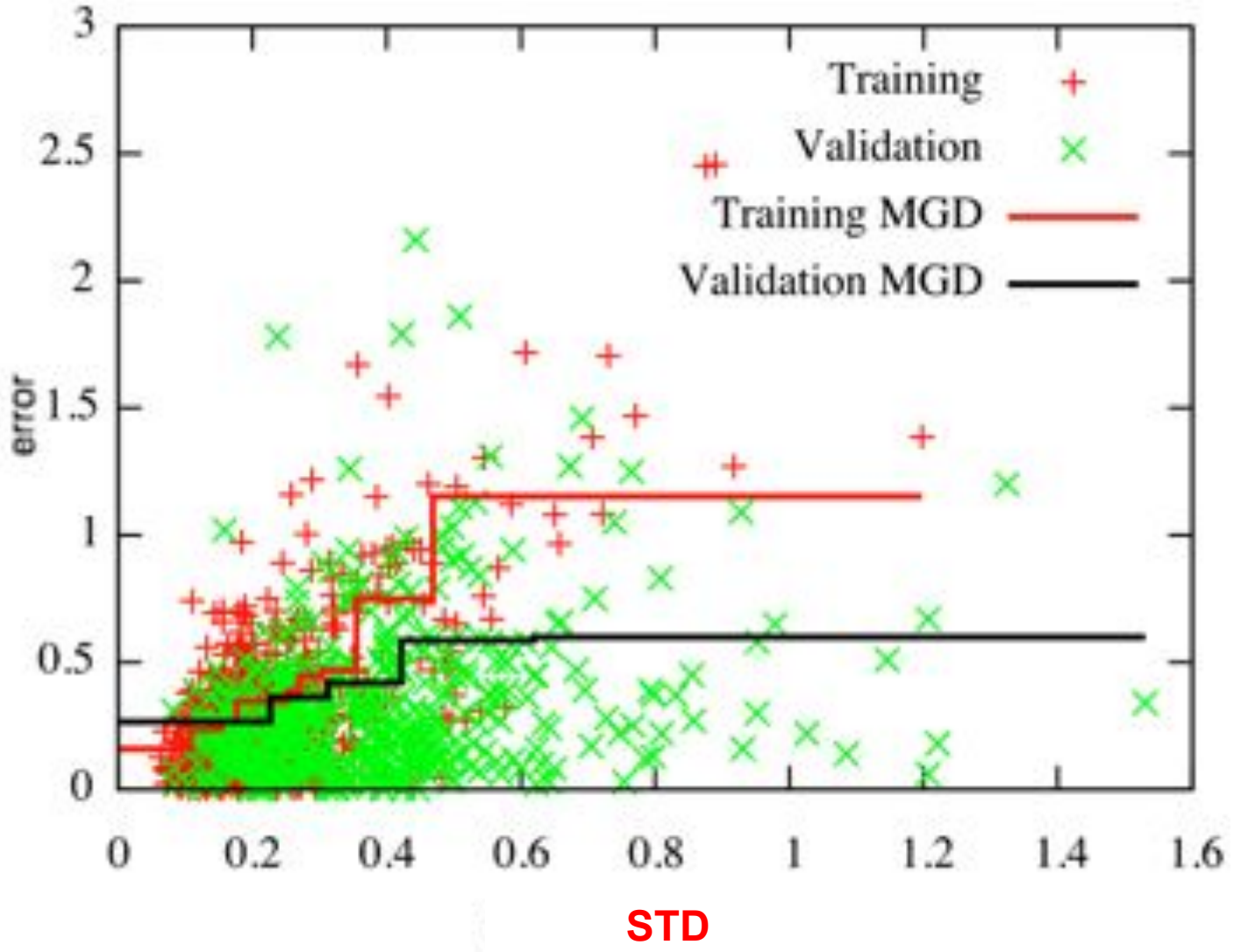
Tetko et al, *J Chem Inf Model*, **2008,** 48(9):1733-46.

Overview of analyzed distances to models (DMs)

EUCLID $EU_m = \frac{\sum_{j=1}^{k} d_j}{k}$ $EUCLID = \overline{EU}_m$ k is number of nearest neighbors, m index of model	**TANIMOTO** $Tanimoto(a,b) = \frac{\sum x_{a,i}x_{b,i}}{\sum x_{a,i}x_{a,i} + \sum x_{b,i}x_{b,i} - \sum x_{a,i}x_{b,i}}$ $x_{a,i}$ and $x_{b,i}$ are fragment counts
LEVERAGE $LEVERAGE = \mathbf{x}^T(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{x}$	**PLSEU** (DModX) Error in approximation (restoration) of the vector of input variables from the latent variables and PLS weights.
STD $STD = \frac{1}{N-1}\sum(y_i - \bar{y})^2$ y_i is value calculated with model i and $\bar{y}$ is average value	**CORREL** $CORREL(a) = \max_j CORREL(a,j) = R^2(\mathbf{Y}^a_{calc}, \mathbf{Y}^j_{calc})$ $\mathbf{Y}^a = (y_1,\ldots,y_N)$ is vector of predictions of molecule i

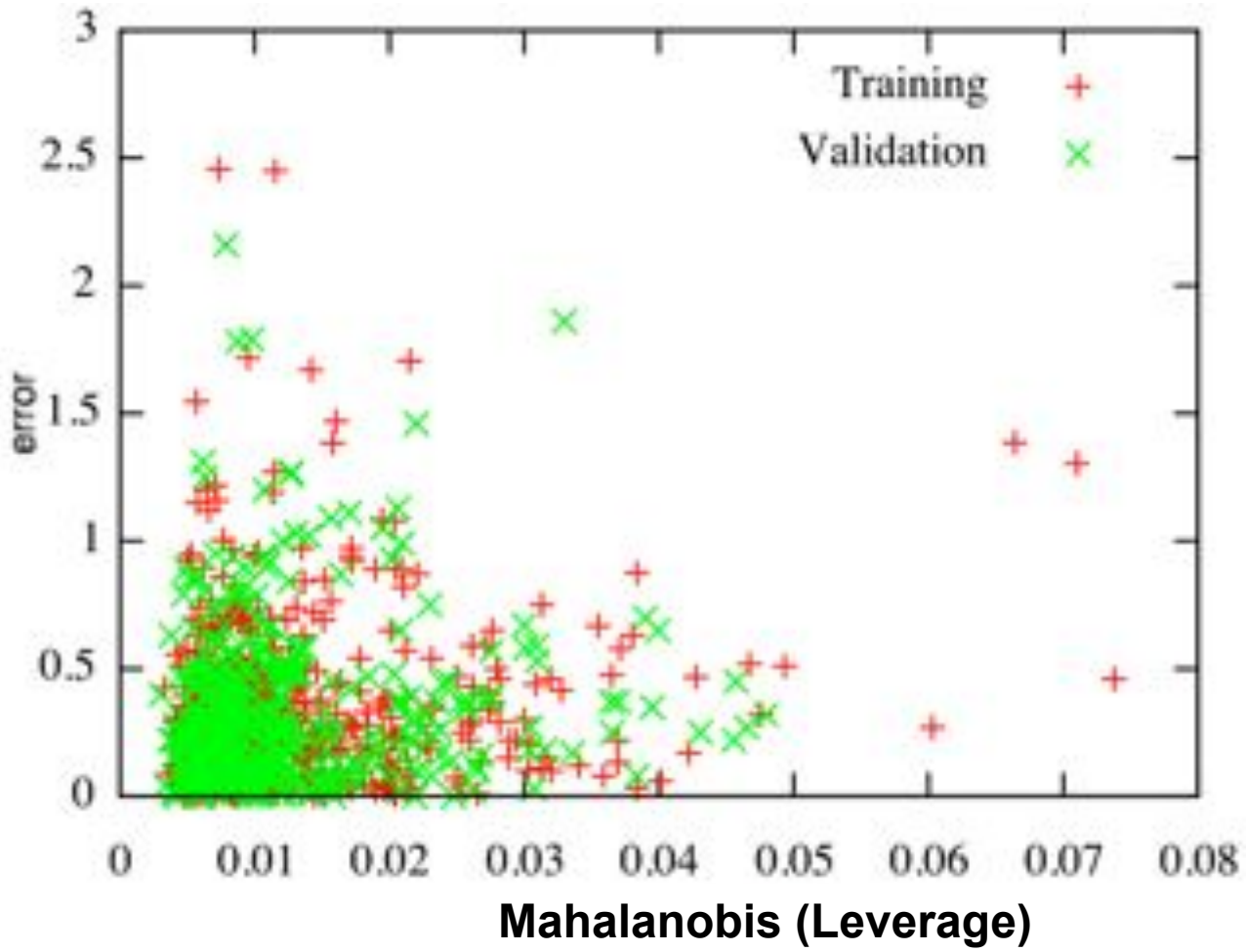
STD

Property-based space: DM does work!



Tetko et al, *J. Chem. Inf. Model*, **2008,** *48*, 1733-46.

Descriptor space: DM does not work



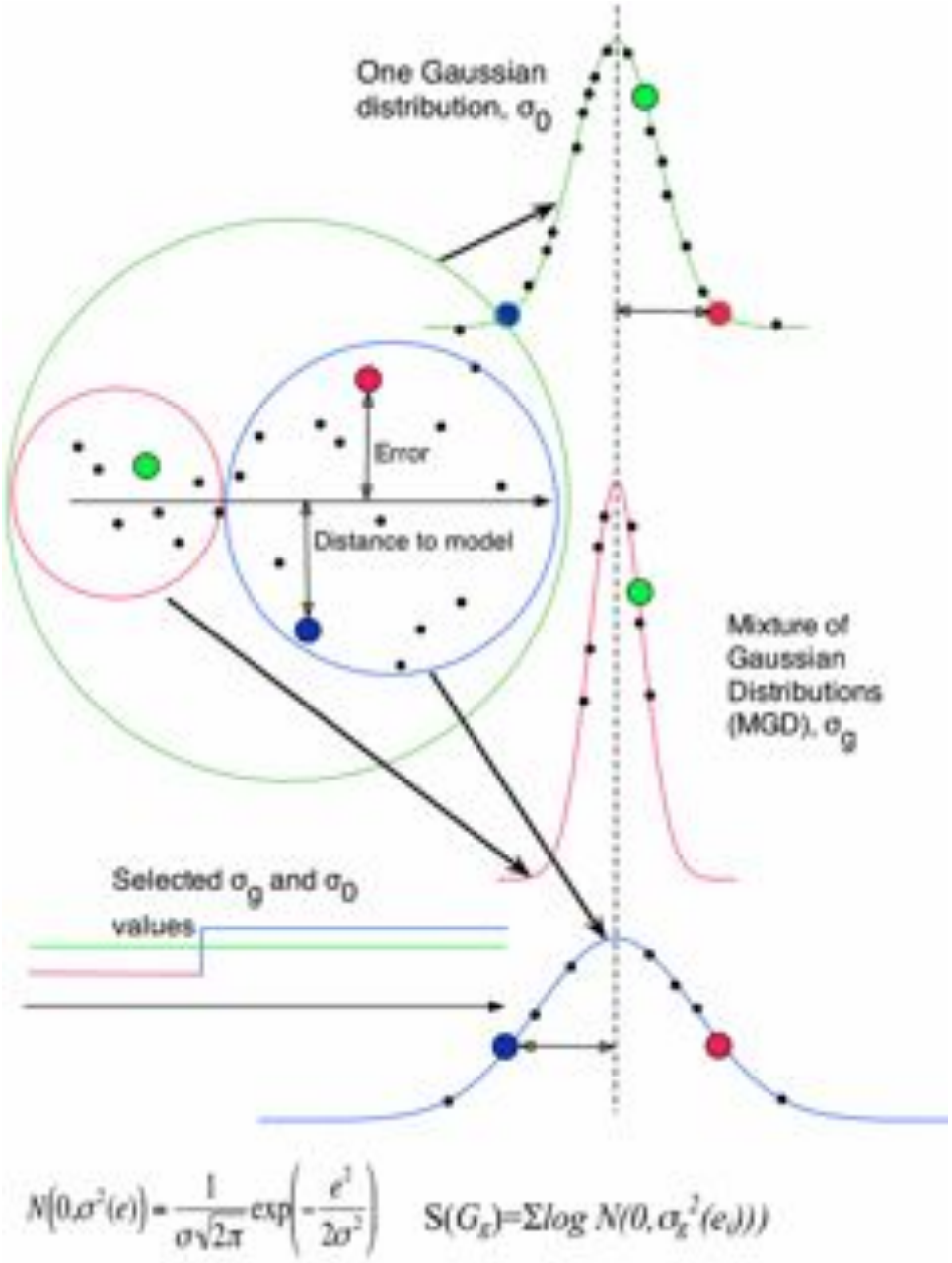
Tetko et al, *J. Chem. Inf. Model*, **2008,** *48*, 1733-46.

Mixture of Gaussian Distributions (MGD)

Idea is to find a MGD, which maximize likelihood (probability)

$\Pi\, N(0, \sigma^2(e_i))$

of the observed distribution of errors



Ranking of Distance to Models (DM)

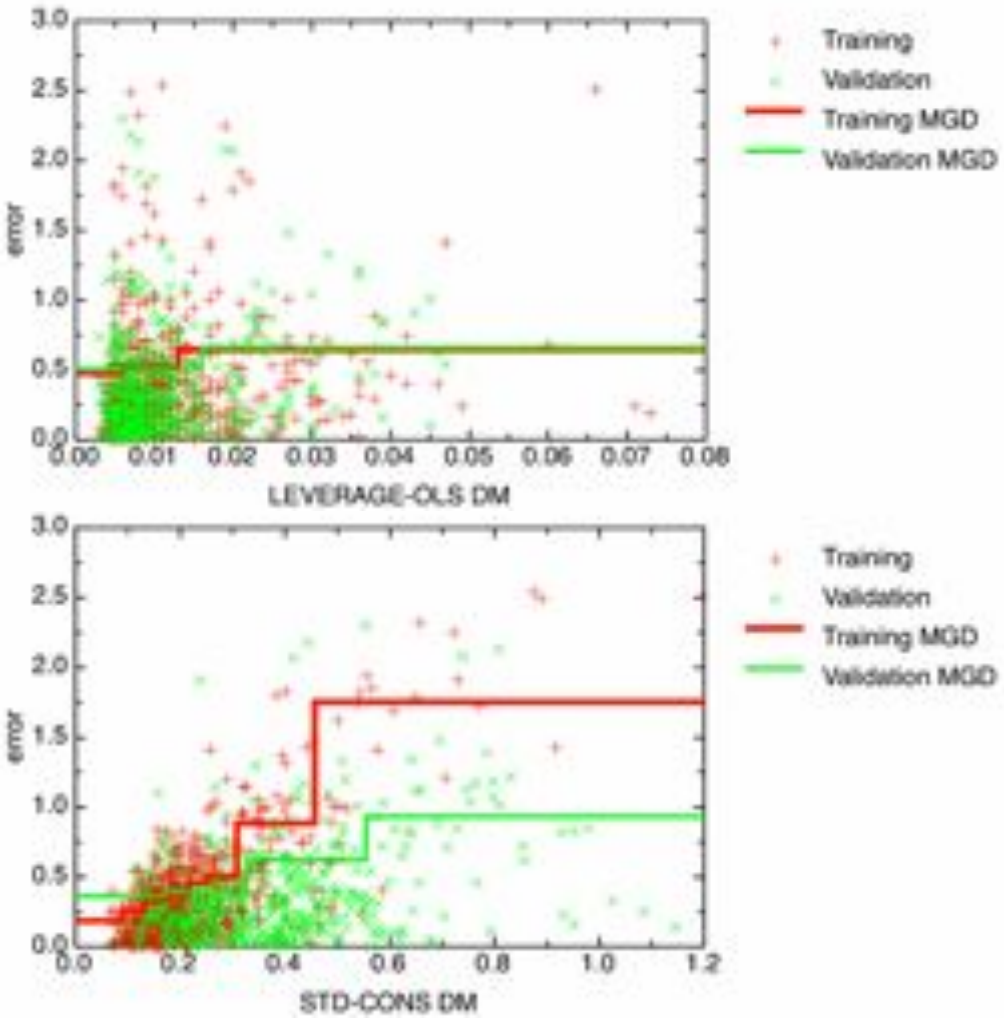
DM	average rank			highest rank[1]		
	LOO	5-CV	**Valid.***	LOO	5-CV	Valid.
STD-CONS	1	1.8	**1.1**	12	2	11
STD-ASNN	2	1.2	**2.5**		10	1
STD-kNN-DR	6.6	4.3	**4.1**			
STD-kNN-MZ	9.2	8.3	**5.3**			
EUCLID-kNN-DR	7.1	4.9	**5.4**			
LEVERAGE-PLS	8.4	5	**6.3**			
EUCLID-kNN-MZ	7.5	7.1	**6.4**			
TANIMOTO-kNN-FR	7	6.1	**6.8**			
TANIMOTO-MLR-FR	8.3	8.3	**9**			
CORREL-ASNN	10.7	10.8	**9.4**			
LEVERAGE-OLS-DR	12.3	12.6	**11.1**			
EUCLID-MLR-FR	7	9.3	**11.5**			
PLSEU-PLS	11.1	11.8	**11.5**			
EUCLID-kNN-FR	12.1	13.3	**12.1**			

*Ordered by performance of the DMs on the validation dataset

Analysis of DMs for a linear model

STD

$Log(IGC_{50}^{-1})=$
-18(±0.7) +0.065(±0.002)**AMR**-
0.50(0.04)**O56**-0.30(0.03)**O58**
-0.29(0.02)**nHAcc**+0.046(0.005)**H-046**+16(0.7)**Me**



The use of various DM provides different discrimination of molecules with low and large errors.

Tetko et al, *J Chem Inf Model*, **2008,** 48(9):1733-46.

2: Benchmarking of logP calculators

Existing Dogma:

- Prediction of physico-chemical properties, in particular **log P**, is simple
- There is no need to measure them
- We have enough number of good computational methods

Is this true?

Data & background models

18 methods (major commercial providers and public software)

in house data:

95809 molecules from Prizer

889 molecules from Nycomed

Arithmetic Average Model (AAM):
mean log*P* was used as a prediction (one value for all molecules)

Rank III: models with errors (*RMSE*) **≥ AAM**, i.e. non-predictive

Rank I: models with *RMSE* identical or close to the best method

Rank II: remaining models

Benchmarking of logP methods for in-house data of Pfizer & Nycomed

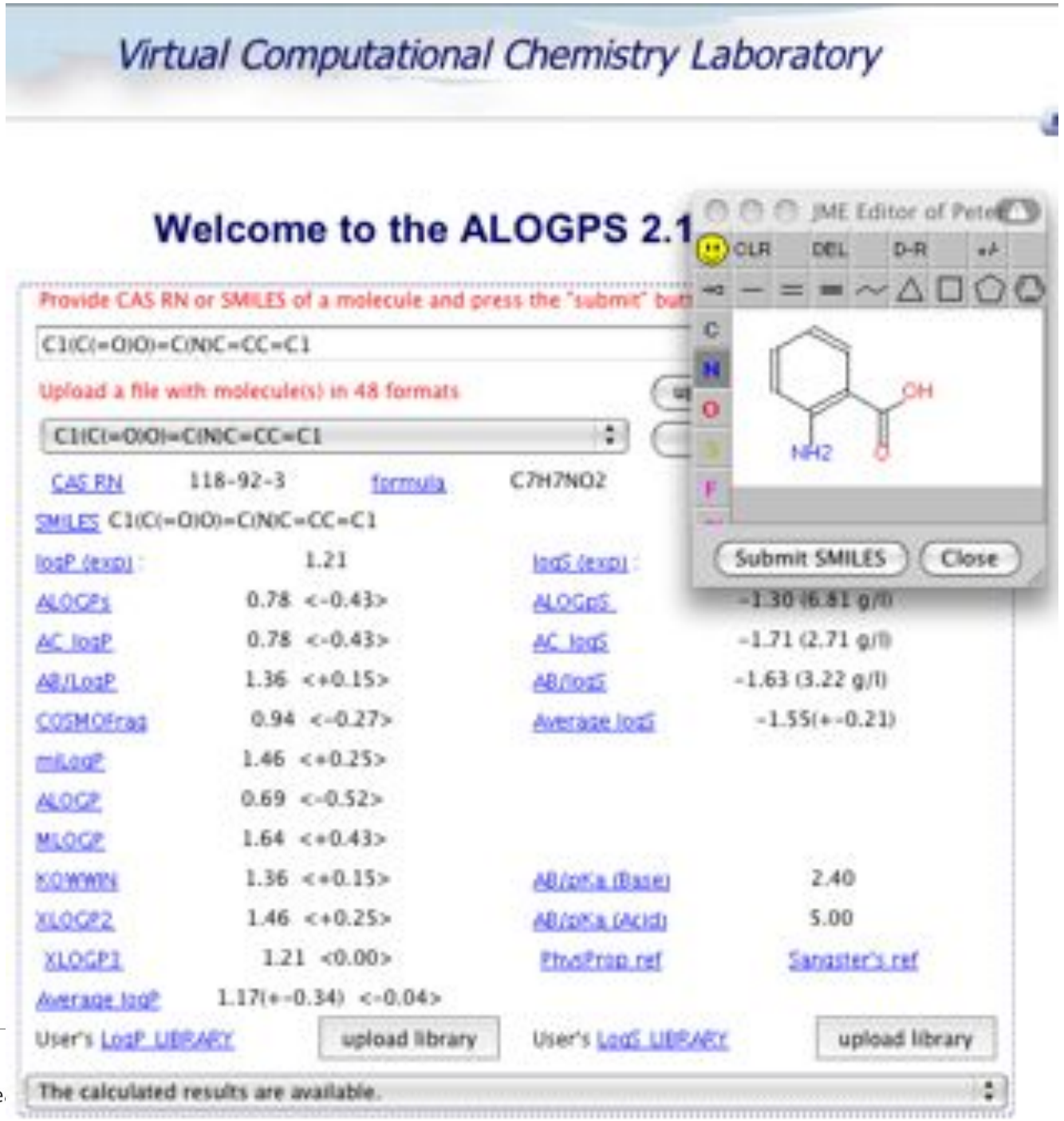
Large number of methods could not perform better than the **AAM** model !

Catastrophe !?

Method	Pfizer set (*N* = 95 809)						Nycomed set (*N* = 882)				
	RMSE	rank	% in error range <0.5	0.5-1	>1	*RMSE, zwitterions excluded*[2]	*RMSE*	rank	% in error range <0.5	0.5-1	>1
Consensus logP	0.95	I	48	29	24	0.94	0.58	I	61	32	7
ALOGPS	1.02	I	41	30	29	1.01	0.68	I	51	34	15
S+logP	1.02	I	44	29	27	1.00	0.69	I	58	27	15
NC+NHET	1.04	II	38	30	32	1.04	0.88	III	42	32	26
MLOGP(S+)	1.05	II	40	29	31	1.05	1.17	III	32	26	41
XLOGP3	1.07	II	43	28	29	1.06	0.65	I	55	34	12
MiLogP	1.10	II	41	28	30	1.09	0.67	I	60	26	14
AB/LogP	1.12	II	39	29	33	1.11	0.88	III	45	28	27
ALOGP	1.12	II	39	29	32	1.12	0.72	II	52	33	15
ALOGP98	1.12	II	40	28	32	1.10	0.73	II	52	31	17
OsirisP	1.13	II	39	28	33	1.12	0.85	II	43	33	24
AAM	**1.16**	**III**	**33**	**29**	**38**	**1.16**	**0.94**	**III**	**42**	**31**	**27**
CLOGP	1.23	III	37	28	35	1.21	1.01	III	46	28	22
ACD/logP	1.28	III	35	27	38	1.28	0.87	III	46	34	21
CSlogP	1.29	III	37	27	36	1.28	1.06	III	38	29	33
COSMOFrag	1.30	III	32	27	40	1.30	1.06	III	29	31	40
QikProp	1.32	III	31	26	43	1.32	1.17	III	27	24	49
KowWIN	1.32	III	33	26	41	1.31	1.20	III	29	27	44
QLogP	1.33	III	34	27	39	1.32	0.80	II	50	33	17
XLOGP2	1.80	III	15	17	68	1.80	0.94	III	39	31	29
MLOGP(Dragon)	**2.03**	III	34	24	42	2.03	**0.90**	III	45	30	25

Mannhold et al, *J. Pharm. Sci.*, **2009**, *98*, 861-893.

http://vcclab.org



ALOGPS 2.1

- LogP: 75 variables,
  12908 molecules,
  RMSE=0.35,
  MAE=0.26

- LogS: 33 variables,
  1291 molecules,
  RMSE=0.49,
  MAE=0.35

Tetko et al, *J. Comput. Aided Mol. Des.* **2005**, 19, 453-63.

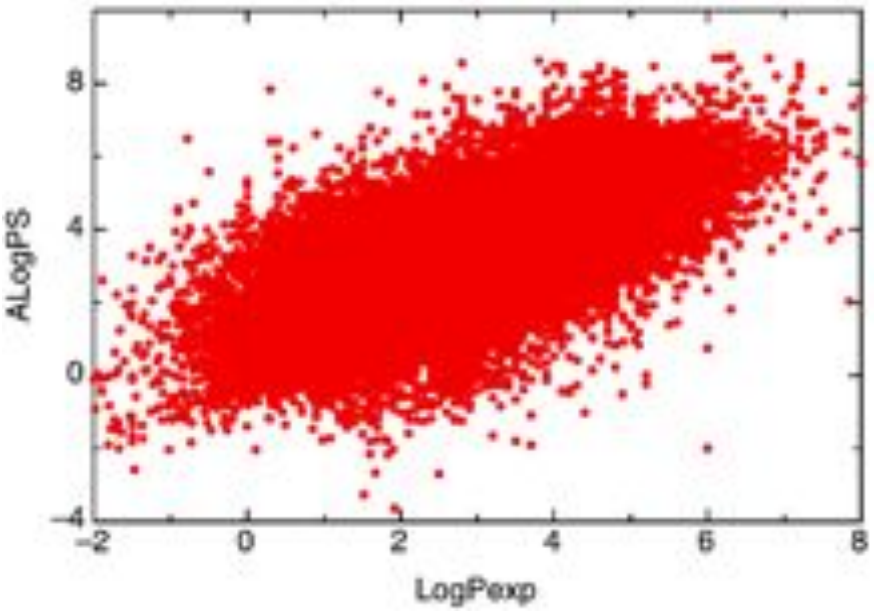
Tetko & Tanchuk, *J. Chem. Info. Comput. Sci.*, **2002**, 42, 1136-45.

CORREL

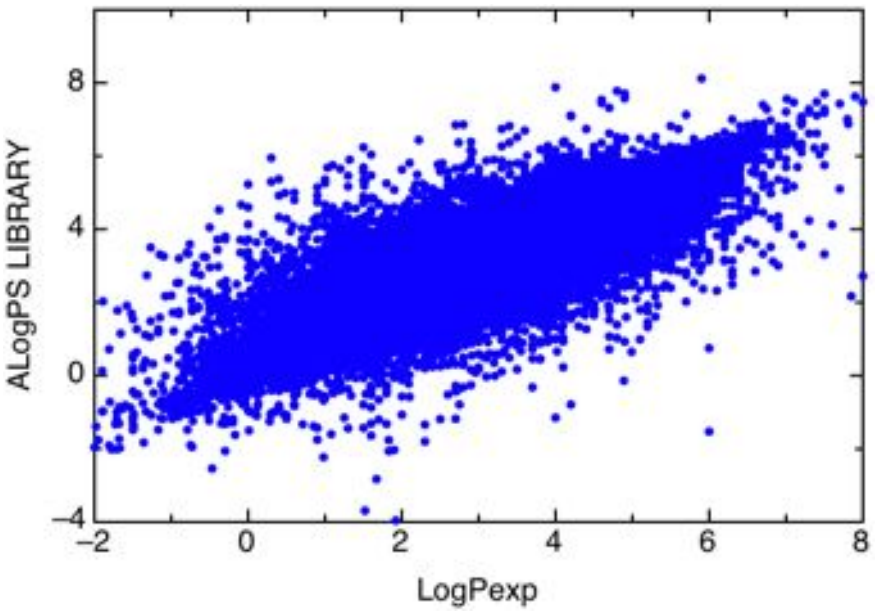
ALOGPS self-learns new data to cover new scaffolds

N=95809 (*in house* Pfizer data)

ALOGPS Blind prediction



ALOGPS LIBRARY

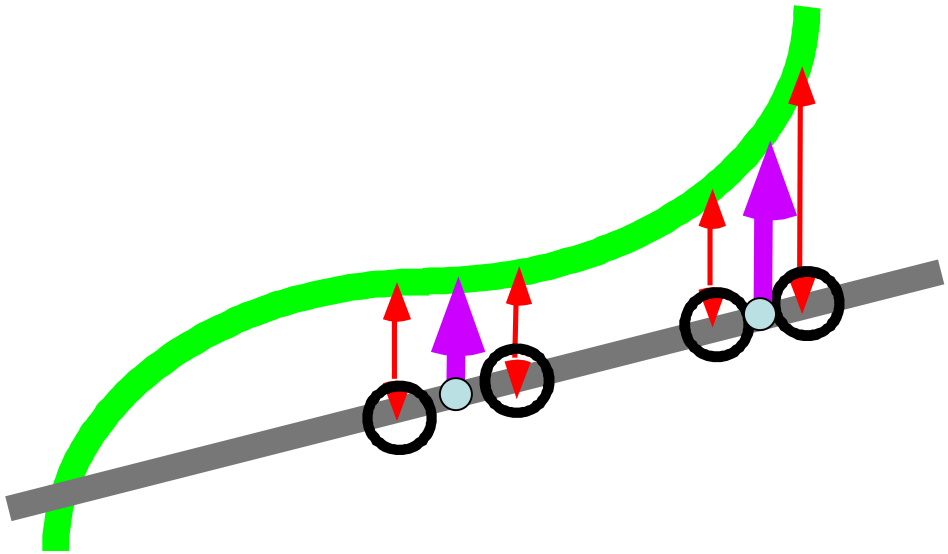


RMSE=1.02 → RMSE=0.59

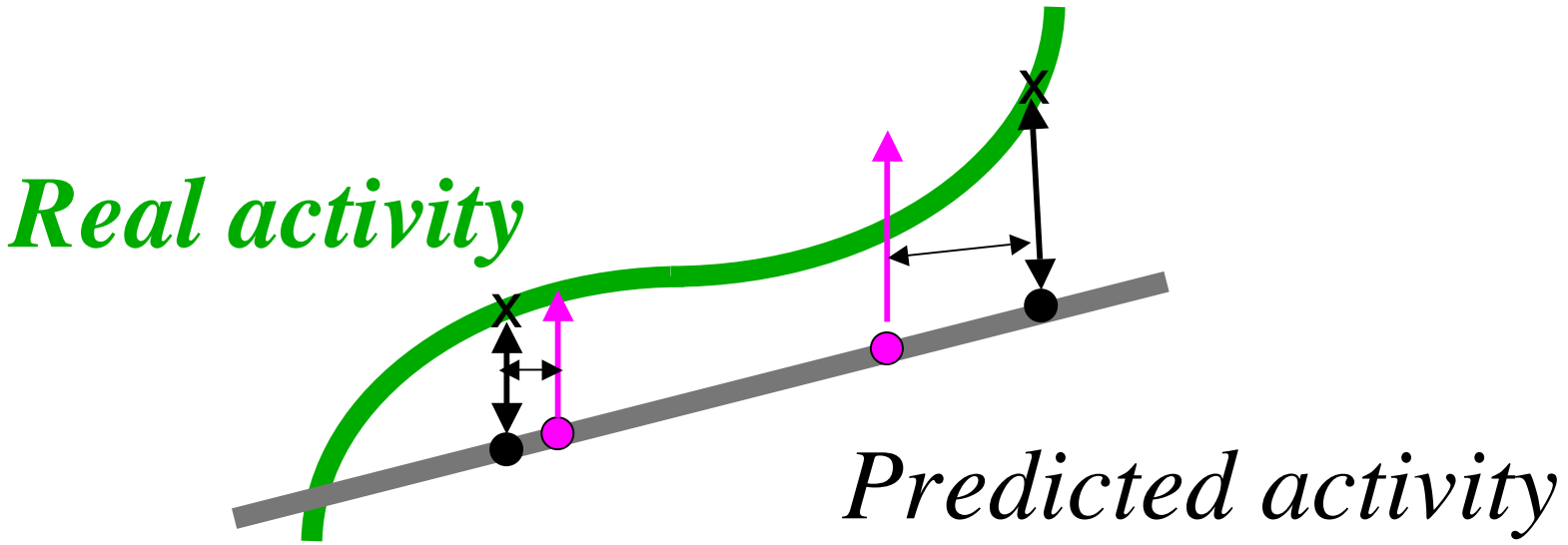
ca 30 minutes of calculations on a notebook!

Tetko et al, *QSAR Comb. Sci.*, **2009**, *28*, 845-9.

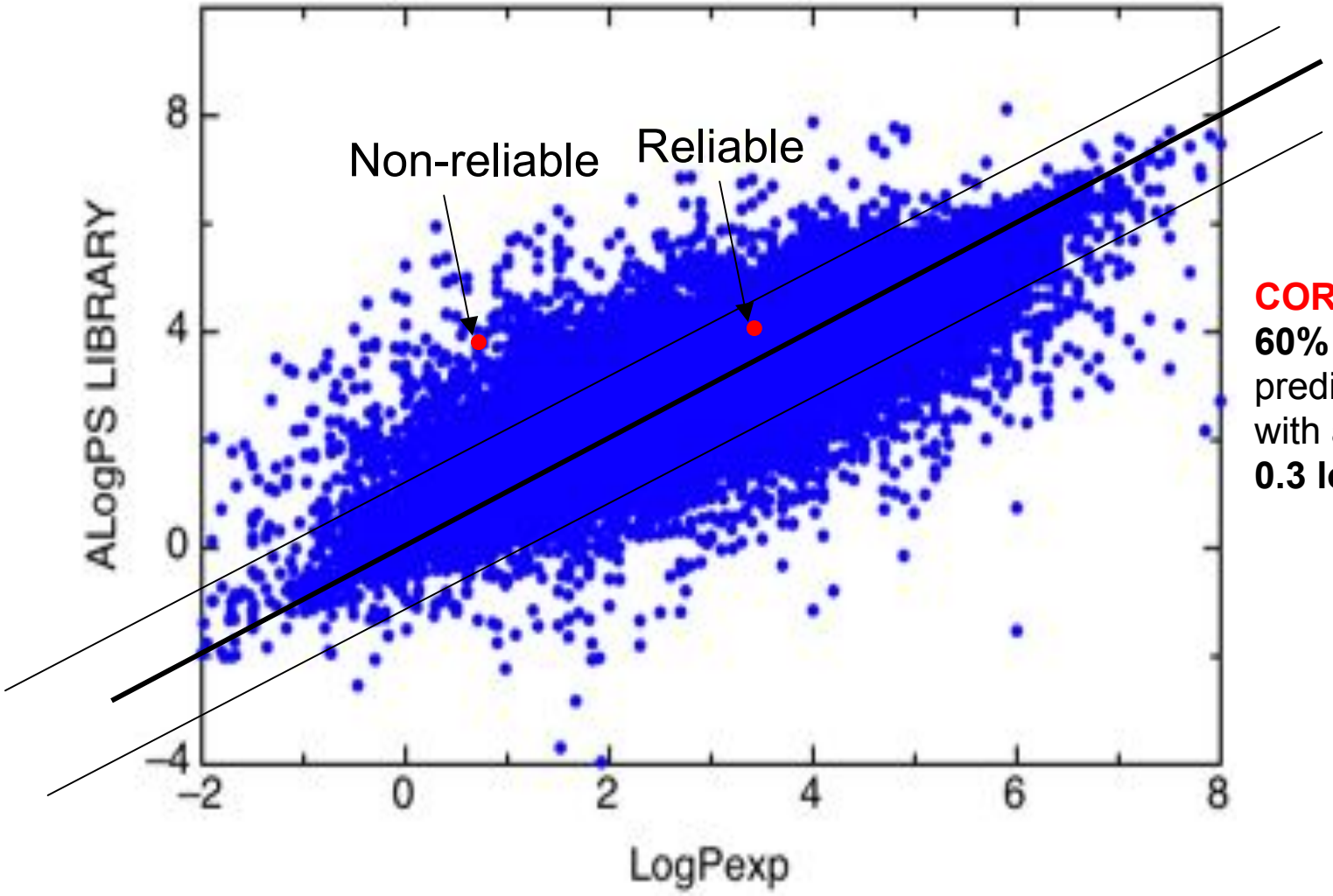
Local correction of a model based on nearest neighbors



Estimation of the model accuracy by the distance to nearest neighbors



ALOGPS distinguishes reliable vs. non-reliable predictions in property-based space (CORREL)



CORREL identifies
60% of molecules
predicted
with average accuracy of
0.3 log units

Tetko et al, *Chemistry & Biodiversity*, **2009**, in press.

CORREL

ALOGPS dramatically improves accuracy

Only reliable predictions (**and we know "who is who"!)** have much higher accuracy.

3: Prediction of Ames Mutagenicity set

http://ml.cs.tu-berlin.de/toxbenchmark

Toxicity against *Salmonella typhimurium*

Data set: 4361 molecules

67% with mutagenic effect (**background model**)

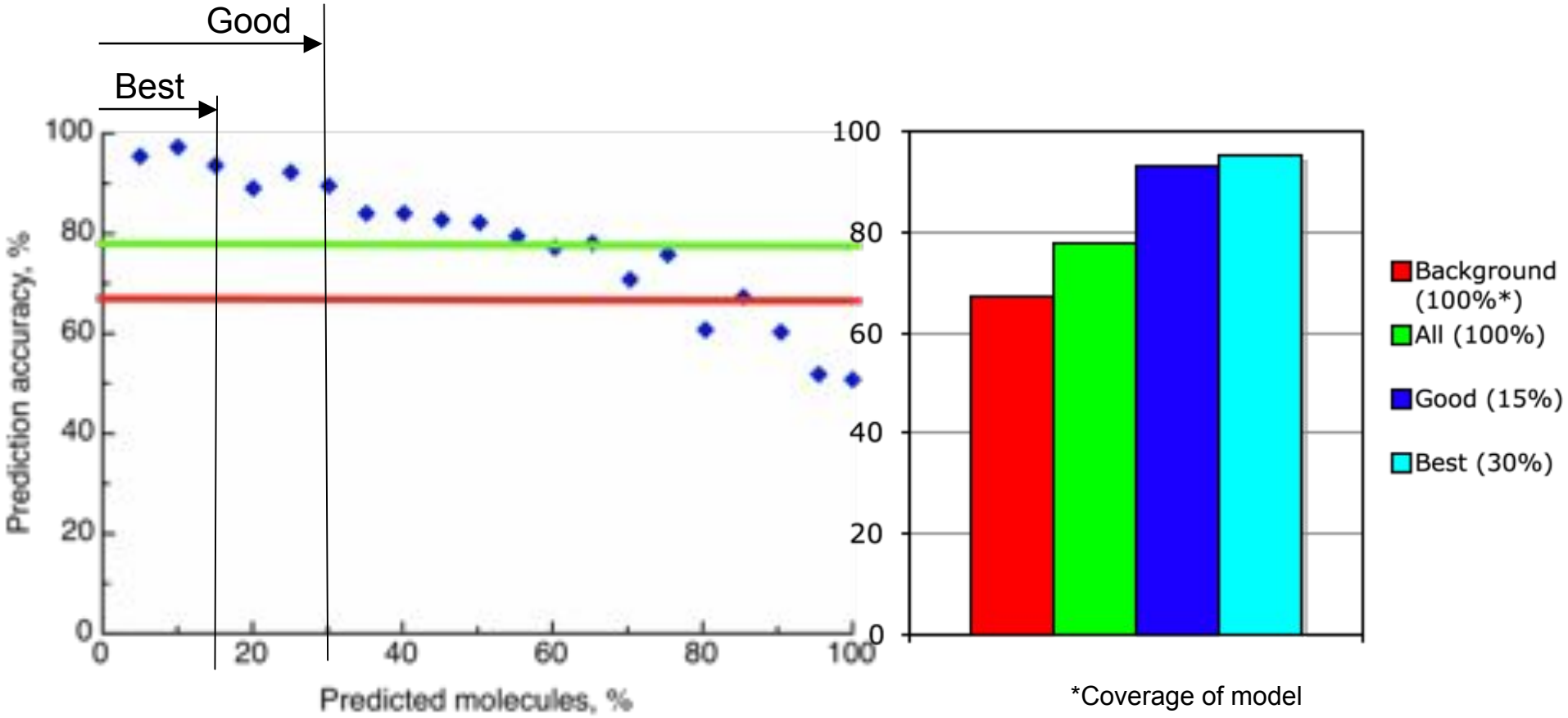
Large international collaboration effort of 13 labs from USA, Canada, EU, Russia, Ukraine & China

Prof. Bruce N. Ames
Inventor of the test (1975)

[1]Schwaighofer et al, *JCIM*, **2008**, 48, 785-96.

STD

Associative Neural Network analysis of Ames set



Only reliable predictions (15% of all data points) are 22%/5% = **4 times** more accurate!

4: Prediction of CYP450 1A2 inhibitors

http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=410

Bioassay AID 410

One of the test performed within NIH Roadmap

4177 active molecules

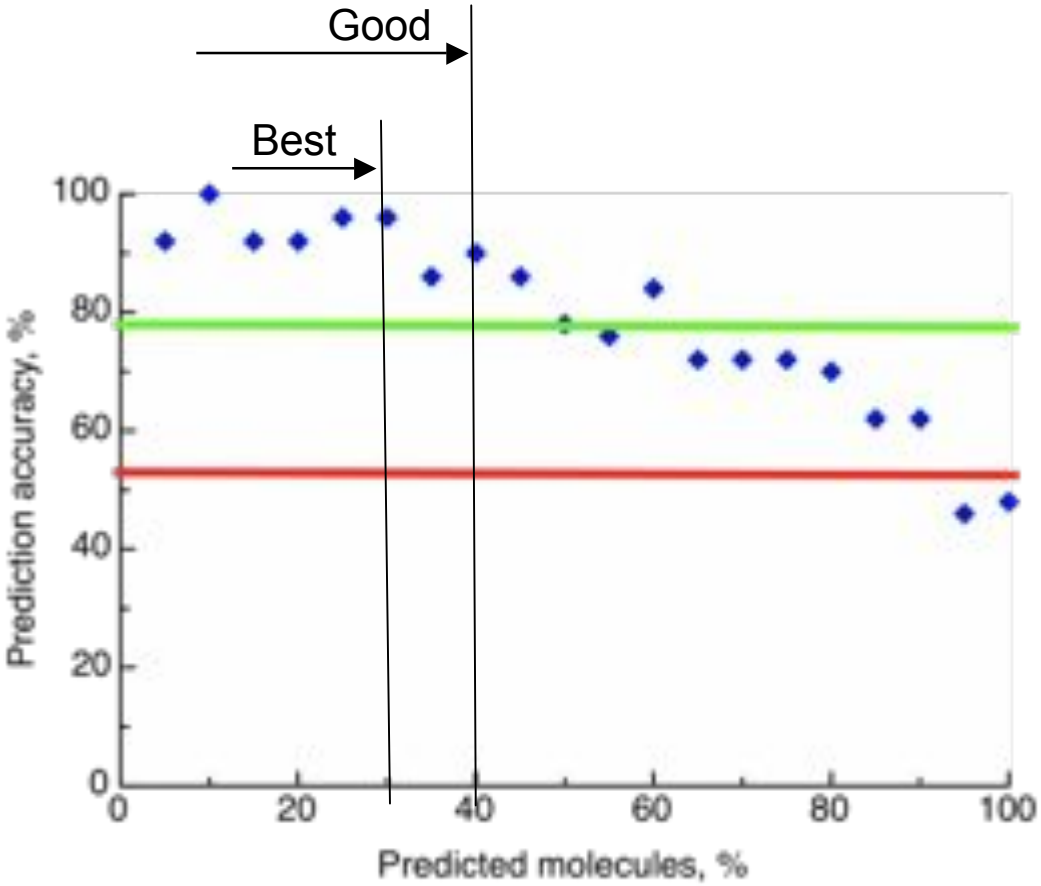
3680 inactive molecules

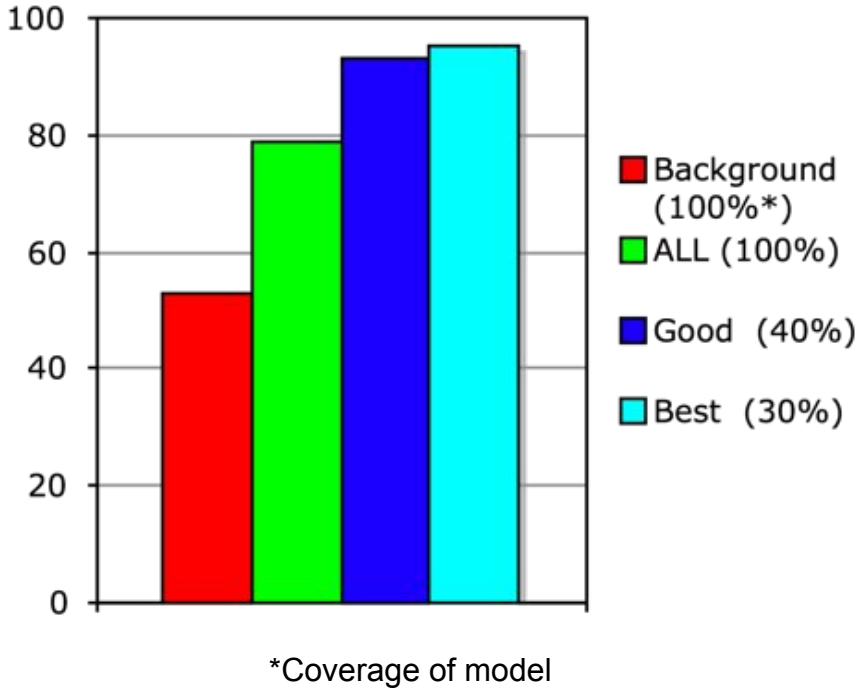
53% were inhibitors of CYP
(**background accuracy**)

Dr. Elias Zerhouni
Former NIH director (2002-2008)

STD

Associative Neural Network analysis of CYP450 set

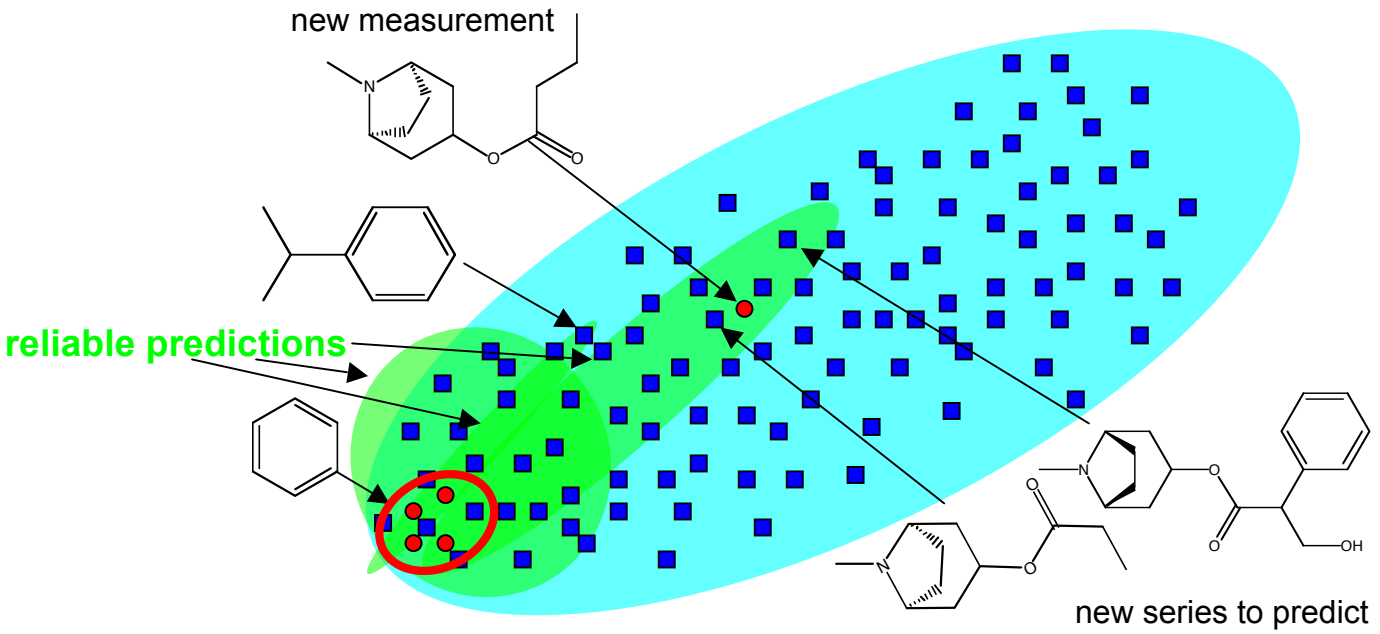




*Coverage of model

The most reliable predictions (30% of all molecules) are 21%/5% = **4 times** more accurate!

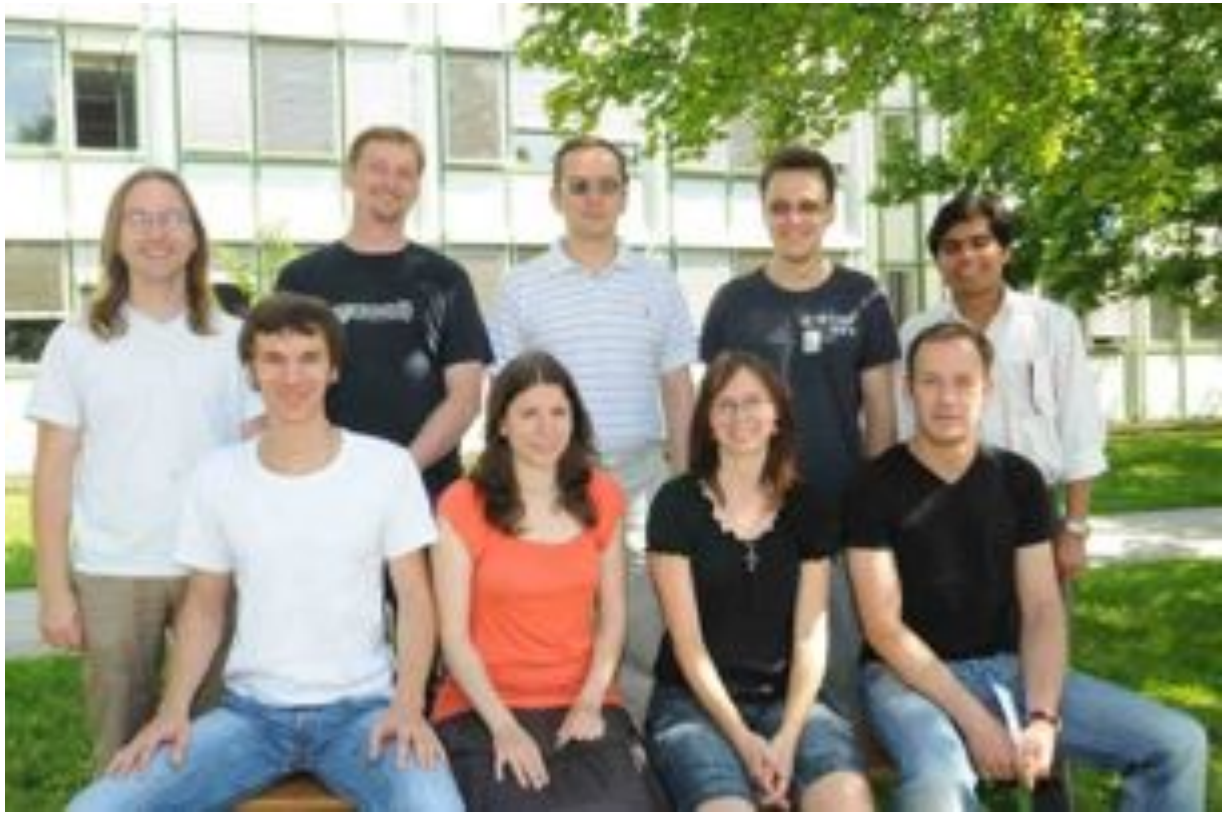
ADMETox and *in silico* challenges



Developed methodology allows navigation in space of molecules with a confidence and:

- ✓ to develop targeted (local) models to cover specific series.
- ✓ to reliably estimate which compounds can/can't be reliably predicted.
- ✓ to provide experimental design and to minimize costs of new measurements.
- ❑ **This is our expertise and "know-how" that we are applying to new data.**

Acknowledgements



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