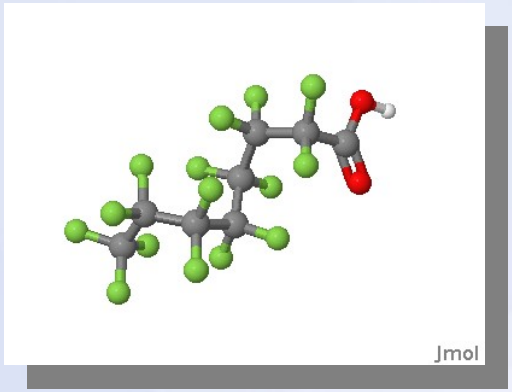

Stepwise D-Optimal design based on latent variables

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Ullrika Sahlin, Tomas Öberg, Igor Tetko

Munich Interact,
Munich, 07.04.2011

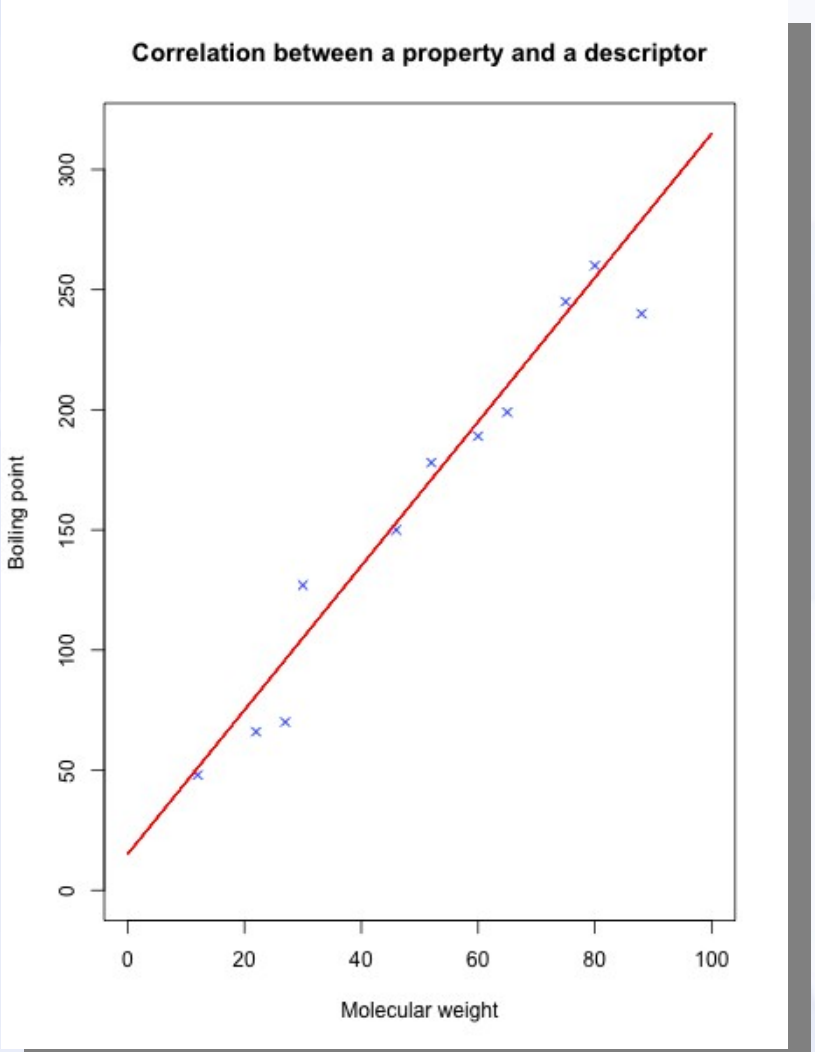
What is experimental design ?

Motivation

- **REACH legislation**: Each chemical compound produced in or imported into the EU in an amount of more than one ton has to be registered according to a number of endpoints
- In case of hazardous, dangerous or toxic compounds, these endpoints contain toxicity and bio-accumulation
- Experimental determination of all these values is often not possible, as experiments consume a lot of time, money - and in case of toxicity – life of animals !
- A valid approach to reduce experiments to a minimum is to test only a small subset of the compounds of interest and to build a reliable QSAR model from them.

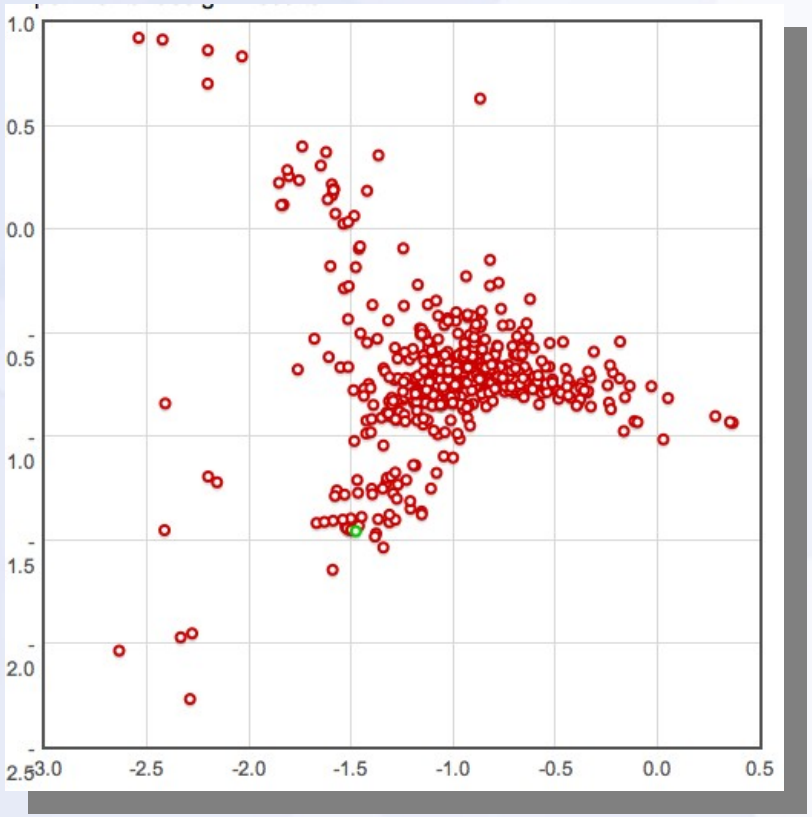
QSAR / QSPR

- QSAR (Quantitative structure-activity relationship) modeling finds the quantitative correlation between molecular structures and a certain property.
- From molecule structure, so called descriptors are calculated (e.g. Molecular weight, number of benzene rings, energy)
- A machine learning algorithm is applied to these descriptors and calculates a model that can be used to predict the property for new compounds



Experimental design

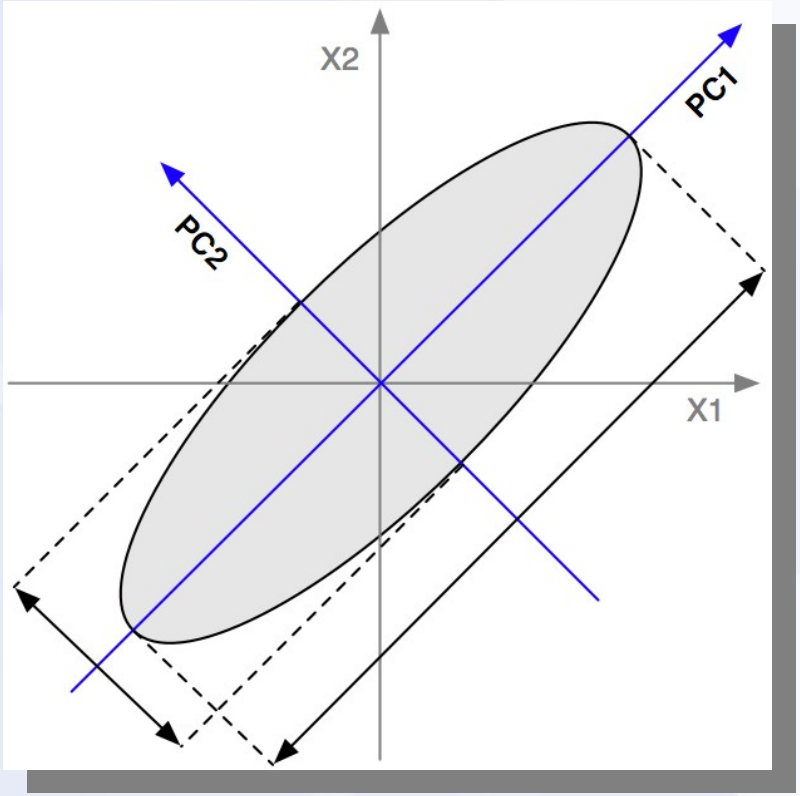
- Given 600 compounds of interest and the limitation to test only 100 of the them, the task is to find a 'good' subset to build a model from.
- But what does 'good' mean ??
  - Avoidance of irrelevant information (outliers)
  - Avoidance of redundant information
  - Selected compounds should be representative



Standard solutions

Standard Solution

- Descriptor calculation for a molecule set
- Multivariate characterization of the compounds using PCA
  - Removal of linear dependencies
  - Decrease in the number of 'descriptors'
- Selection of testing subset (e.g. with D-Optimal algorithm)
- Testing of compounds
- Model building with linear regression algorithm

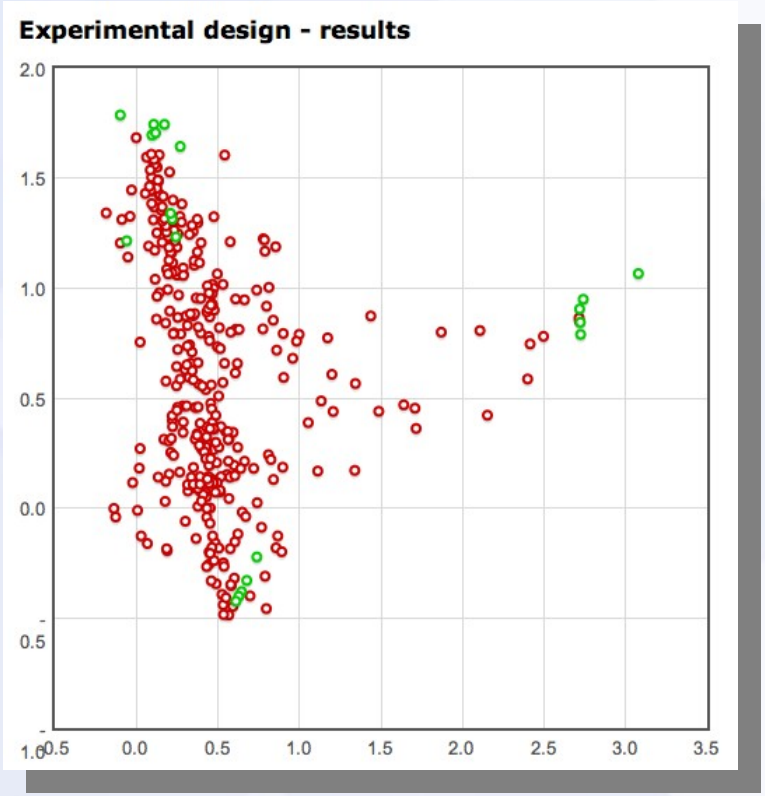


Marcos M. Campos: Oracle Data Mining and Analytics

Marcos M. Campos: Oracle Data Mining and Analytics

Problems

- Different descriptors deliver different outliers, as they are grouping molecules only by certain aspects
- Globally relevant descriptors might be irrelevant for local models
- There is no guarantee, that principal components correspond to or correlate with the property focussed on
- Principal components can display noise, as long as it has just a high variance
- Principal components are not specific for a certain endpoint



- D-Optimal Design works like outlier detector

Stepwise PLS-based strategy

PLS-based adaptive strategy I

- Because of restricted capacities, labs usually do not test all compounds in parallel but in a stepwise procedure
- The information gathered in each step can be used to refine the selection of compounds
- PLS combines linear regression with PCA
- Correlation to the target property is taken in consideration
- PLS delivers so called 'latent variables' instead of principal components to build a new vector base
- Removal or at least decrease of noise

PLS-based adaptive strategy II

- Based on D-Optimal design selection algorithm
- Utilizing Partial Least Squares (PLS) techniques to retrieve latent variables

1) Select an initial set of compounds with a traditional D-Optimal approach, based on principal components
2) Build a PLS regression model on the tested data
3) Use this model to calculate the latent variables for all compounds
4) Expand the selected set by applying the D-Optimal approach to the latent variables instead of principal components
5) Repeat steps 2) – 4) as often as required

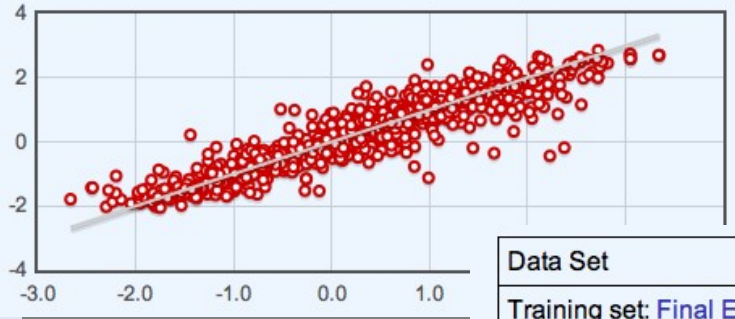
Validation

Datasets

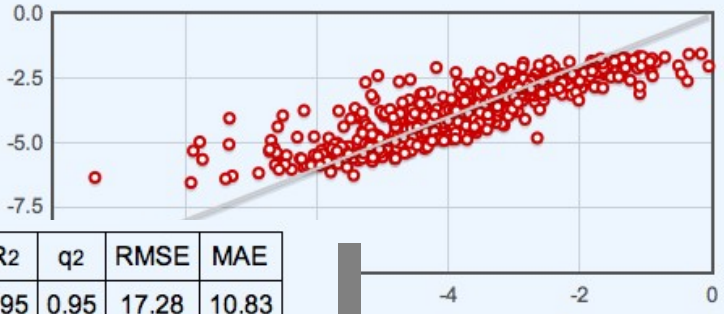
	Endpoint	Instances	Structural restrictions	Intricacy of endpoint	Model quality
LogKOC	Partition coefficient	668	no	medium	average
Boiling Point		699	muted	low	high
Density	Mass per volume	142	yes	low	high
IGC50	Toxicity on T. pyriformis	1158	no	high	good
LC50	Toxicity on fathead minnow	579	no	high	average

Models

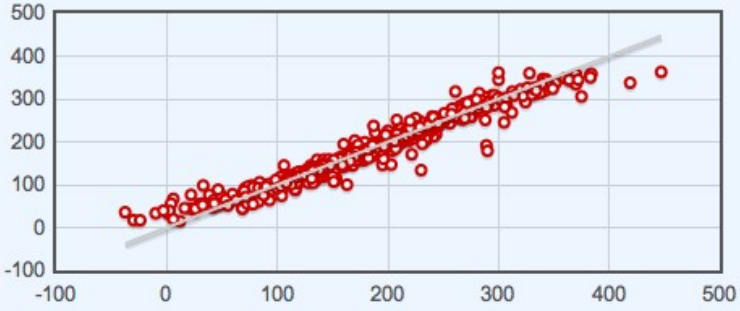
Data Set	R2	q2	RMSE	MAE
Training set: Final ED lGC50 (1158 records)	0.86	0.86	0.41	0.28



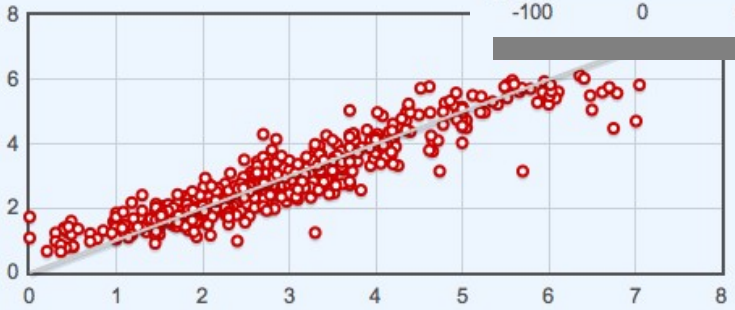
Data Set	R2	q2	RMSE	MAE
Training set: Final ED LC50 (579 records)	0.72	0.72	0.73	0.53



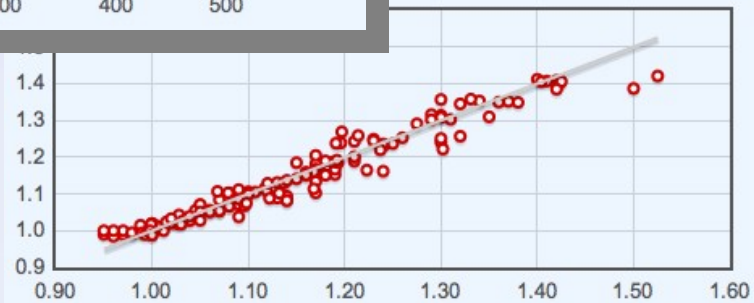
Data Set	R2	q2	RMSE	MAE
Training set: Final ED BP (699 records)	0.95	0.95	17.28	10.83



Data Set
Training set: Final ED LogKOC (668 re



	R2	q2	RMSE	MAE
(142 records)	0.95	0.95	0.03	0.02

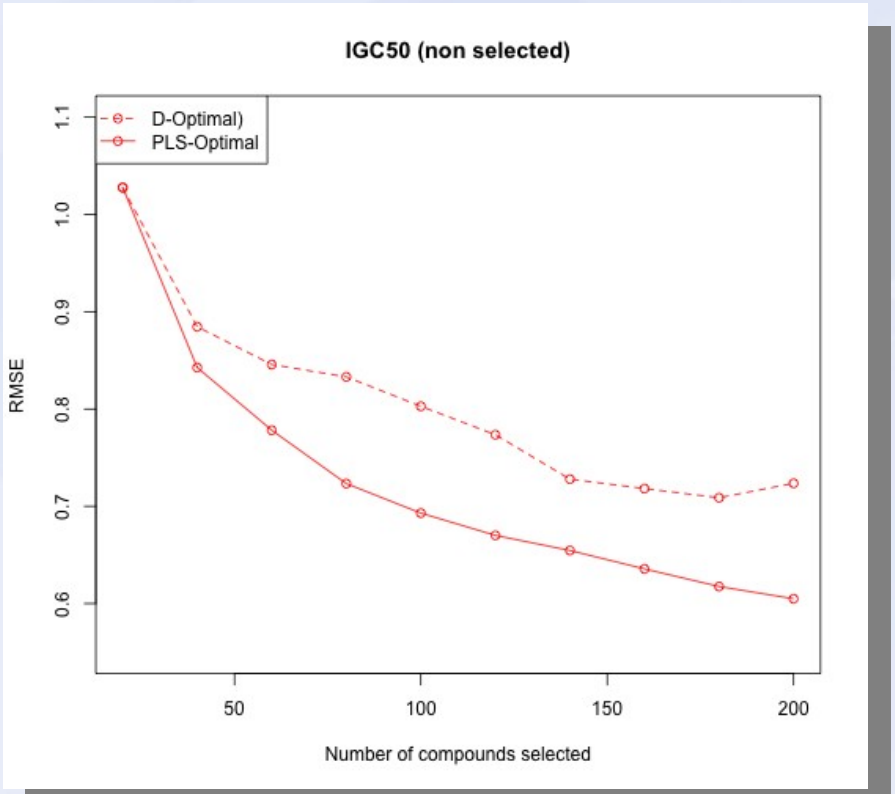


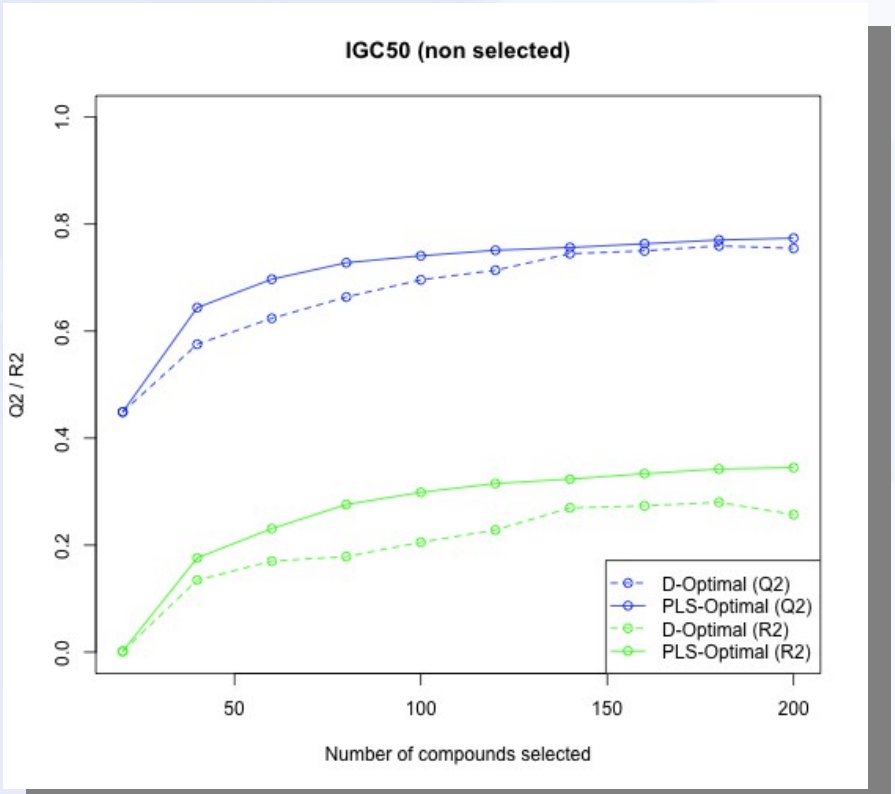
Validation pipeline

- Descriptor calculation
  - AlogPS, Estate indices, ISIDA fragments (length 2-5)
- 100 splits on each dataset
  - 70% of compounds as operative set on which the design is performed
  - 30% of compounds as external validation set
- Comparison of the performance
  - **D-Optimal** vs. **Stepwise PLS-Optimal**
  - Comparison for a range of 20 to 200 selected compounds
  - 20 new compounds selected in each PLS-Optimal step
  - Validation on the operative set, the operative set without selected compounds and the external validation set

Results

Results I


IGC50 (non selected)
D-Optimal)
PLS-Optimal
RMSE
0.6
0.7
0.8
0.9
1.0
1.1
50
100
150
200
Number of compounds selected


IGC50 (non selected)
Q2 / R2
0.0
0.2
0.4
0.6
0.8
1.0
50
100
150
200
Number of compounds selected
D-Optimal (Q2)
PLS-Optimal (Q2)
D-Optimal (R2)
PLS-Optimal (R2)

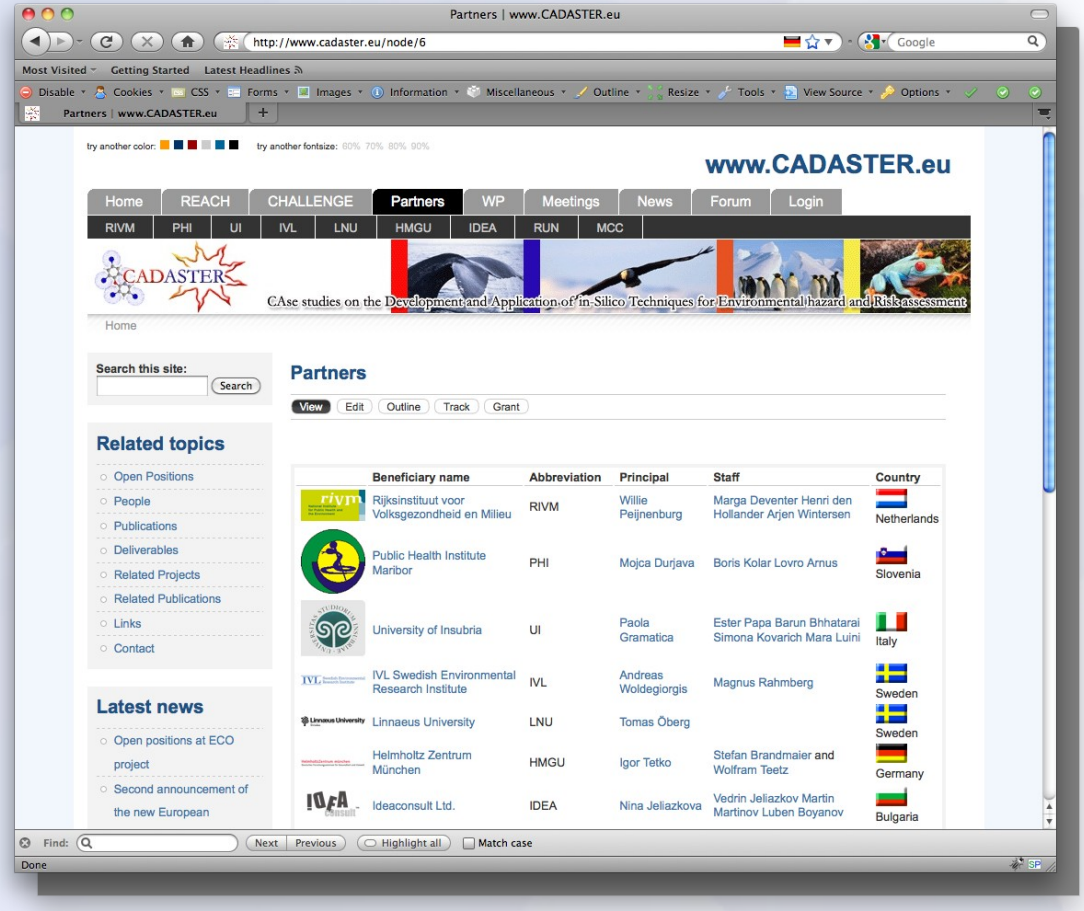
Results II

- Improvement of performance is **highly significant** ($p(h0) < 0.001$, binomial test) concerning
  - RMSE (up to 18%)
  - Q2 and R2
- for
  - all tested endpoints
  - both external and internal validations
  - each size of the datasets
  - the full range from 5% to 25% selected points
- Models of equal performance can be created with only 50% of compounds

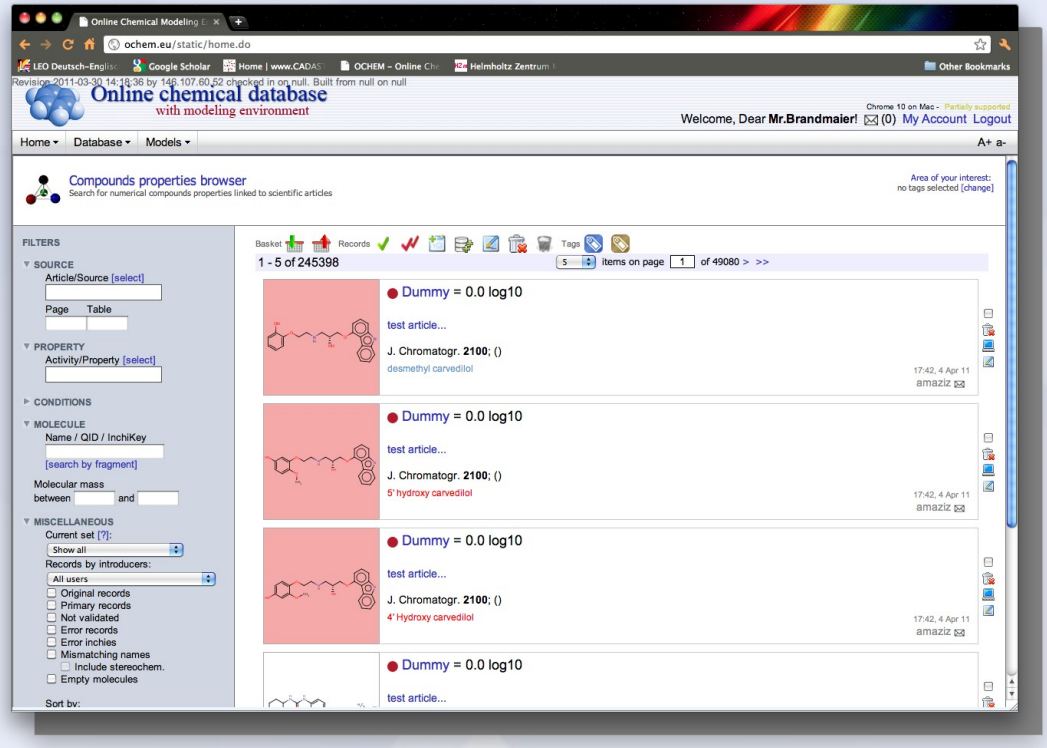
Anything more ???

CADASTER

- FP7-funded EU project
- Implementation of REACH legislation to register chemical compounds
- Risk assessment for chemicals belonging to four compound classes
- Nine institutes from seven countries



Modeling platform Ochem.eu

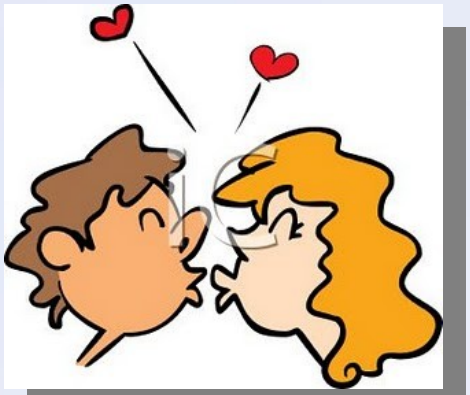


- Containing 245398 measured values from literature
- Implementation of many machine learning algorithms
- Calculation of 20 different descriptor sets
- Various filtering options
- Application of peer reviewed published models
- Flexible management for endpoints
- All experimental conditions can be added to a record (unique feature)

Take home message

- Principal components are not necessarily correlated with the target property
- Stepwise approaches can be used to iteratively refine the design
- The usage of PLS latent variables instead of principal components can significantly improve the performance of experimental design

Experimental design makes three creatures happy:



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