WORKSHOP ON QSAR MODELS FOR REACH

Mario Negri Institute, Milan, Italy - March 10-11, 2009

SIXTH FRAMEWORK PROGRAMME

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KnowledgeMiner Software

Enhancing CAESAR Models

http://www.caesar-project.eu/

High Value Properties of CAESAR Models

- High quality of data
- Out-of-sample validation of models
- Reproducibility
- Transparency
- Application domain
- Ready- and Easy-to-use

Visions for CAESAR Models

Implementation of
Hybrid models from existing models
Prediction interval and uncertainty
Optimisation according to FN and FP costs

Hybrid QSAR Models: Motivation

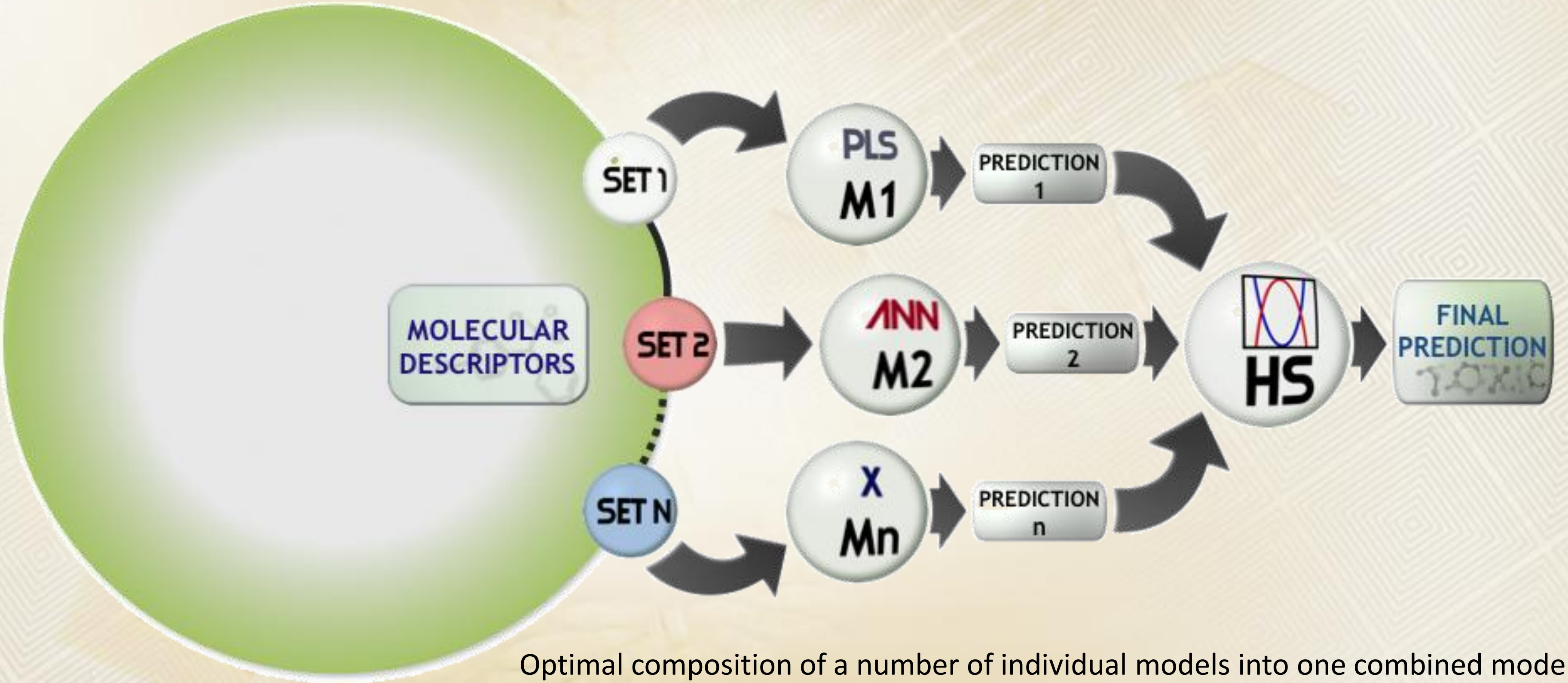
- On noisy, uncertain data sets a number of models can be built, which are comparable with respect to prediction accuracy. (in CAESAR: ≈ 25 / endpoint)
- Commonly, a model is a simplified reflection of the complex reality, only. It describes a specific part of the object's behavior.

So why only use one model?

Hybrid QSAR Models: Motivation

- A *more complete reflection of the reality* can be obtained when combining several models:
  - Different modeling approaches
  - Different input data
  - Different parameters
- *Increased prediction accuracy* of up to about 10% is possible.

Hybrid QSAR Models: Principle



Optimal composition of a number of individual models into one combined model

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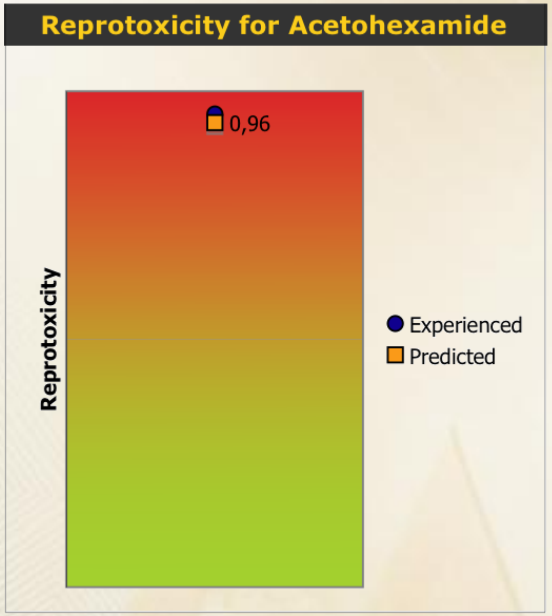
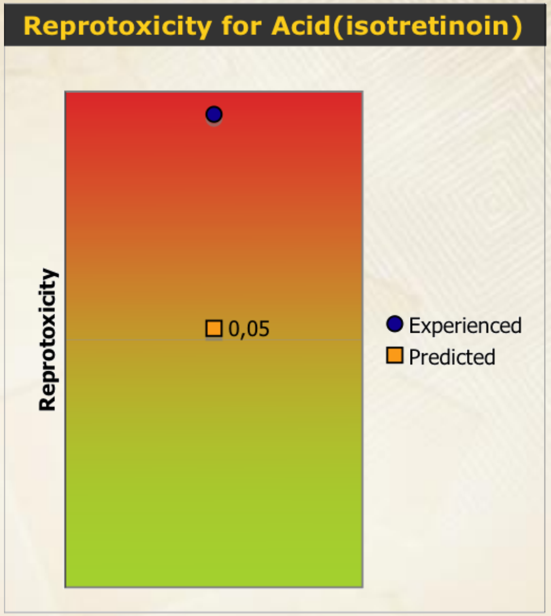
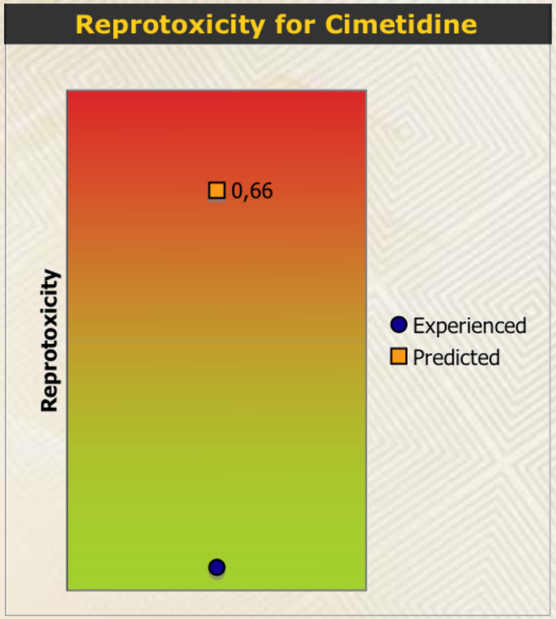
Prediction: Commonly







Regression models

Predicted Class Value	Predicted Class Value	Predicted Class Value
reprotoxic	reprotoxic	reprotoxic

Class. models

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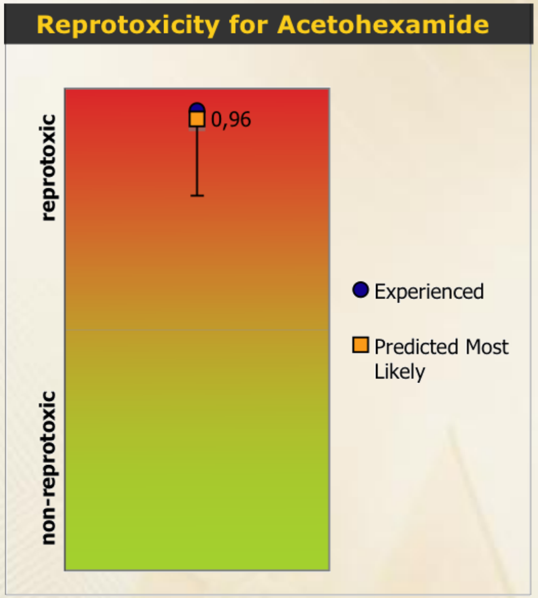
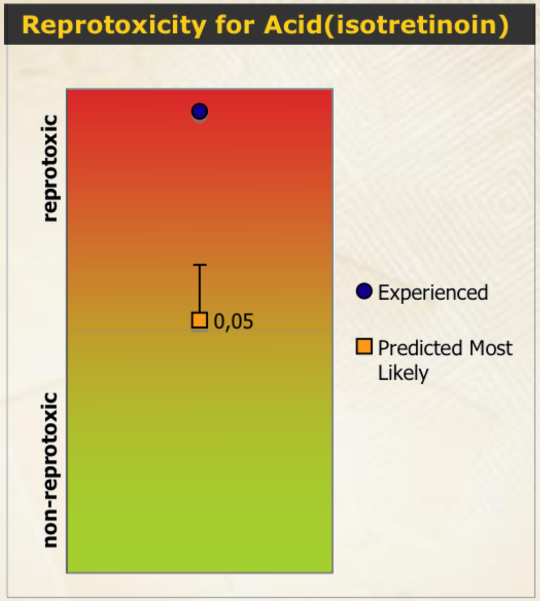
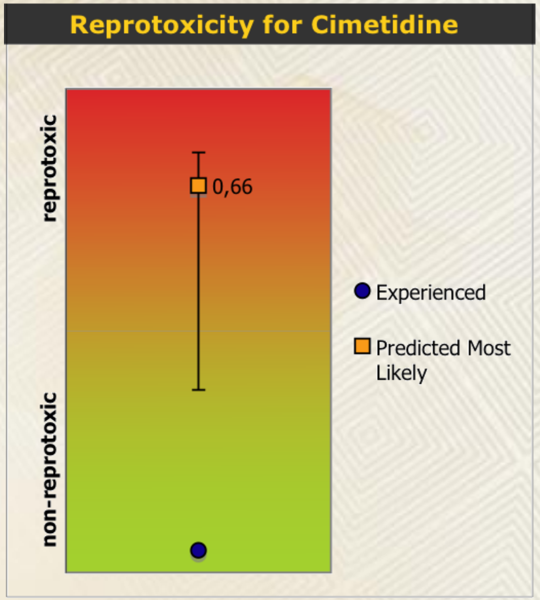
*) the values shown do not necessarily correspond to the final model for developmental toxicity.

Prediction Interval







Classification and regression models

Per compound prediction uncertainty available for decision-making

Freedom of choice

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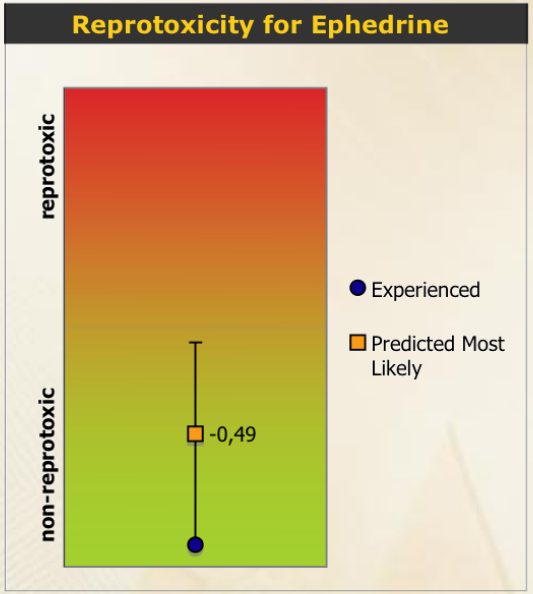
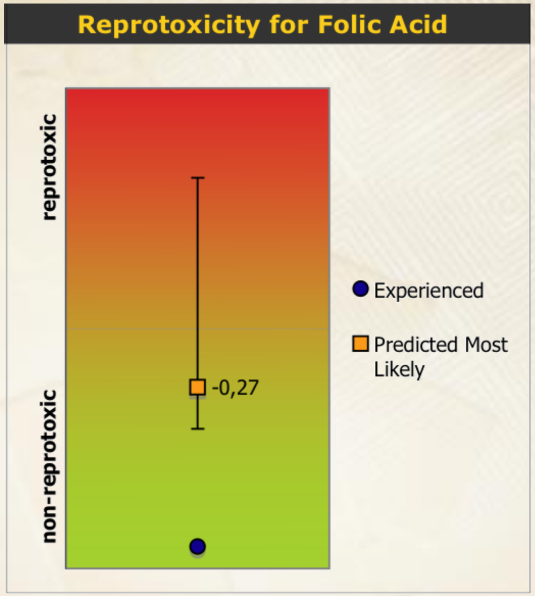
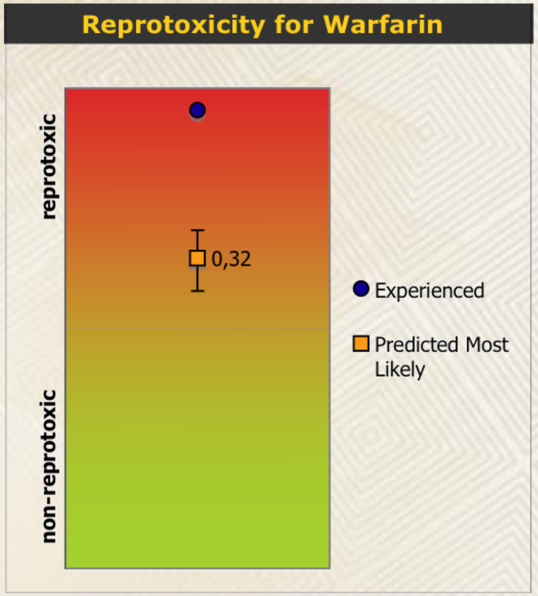
Prediction Interval







Classification and regression models

Uncertainty is huge for experimental data, already.
We cannot expect QSAR models built on this data *being less uncertain* than the original information is.

*) the values shown do not necessarily correspond to the final model for developmental toxicity.

Visions for CAESAR Models

Implementation of
Hybrid models from existing models
Prediction interval and uncertainty
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Classification: Current Praxis

Given: Data set of experimental values about carcinogenicity (the „Truth“)
100 compounds are carcinogenic (Positive)
100 compounds are not carcinogenic (Negative)

Balanced classifier		
Confusion Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	74	25
Predicted: Negative	26	75

→

Accuracy	74,5 %
Sensitivity	74 %
Specificity	75 %

Balanced sensitivity and specificity

Cost-sensitive Models

What if there are *different costs* for misclassified compounds (FP/FN) and/or *different benefits* for correctly classified compounds (TP/TN)? → **Real-world scenario**

High relative False Negative costs		
Cost-Benefit Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	0	1
Predicted: Negative	9	-3

&

Balanced classifier		
Confusion Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	74	25
Predicted: Negative	26	75

Cost/compound	0,09	**Relative cost**	3,2%

Cost-sensitive Models

Using a *cost-sensitive approach* to find the **optimal classifier** for cost-benefit matrix:

False Negative Optimisation

High relative False Negative costs		
Cost-Benefit Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	0	1
Predicted: Negative	9	-3

&

False Negative optimised classifier		
Confusion Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	89	42
Predicted: Negative	11	58

Benefit/compound	0,22	**Relative benefit**	11,8%

Cost-sensitive Models

How does the balanced classifier perform in the **inverse situation**?

False Positive Optimisation

High relative False Positive costs		
Cost-Benefit Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	-3	9
Predicted: Negative	1	0

&

Balanced classifier		
Confusion Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	74	25
Predicted: Negative	26	75

Cost/compound	0,14	**Relative cost**	5,6%

Cost-sensitive Models

Using a *cost-sensitive approach* to find the **optimal classifier** for cost-benefit matrix:
False Positive Optimisation

High relative False Positive costs		
Cost-Benefit Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	-3	9
Predicted: Negative	1	0

&

False Positive optimised classifier		
Confusion Matrix	**Truth: Positive**	**Truth: Negative**
Predicted: Positive	70	21
Predicted: Negative	30	79

Benefit/compound	0,02	**Relative benefit**	1,8%

Cost-sensitive Models

One Example QSAR Model		
Summary Benefits	**Balanced Classifier**	**Optimised Classifier**
FN Minimisation	-3,2 %	11,8 %
FP Minimisation	-5,6 %	1,8 %
Balanced	24,1 %	24,1 %

Values in one column are not comparable
since based on different cost-benefit matrices.

Cost-sensitive Models

- Apparently, there is an **optimal classifier** for given cost-benefit matrix and model; balanced classifier optimal only for balanced costs/benefits
- **Objective** *accuracy- and cost-driven optimisation* of FP or FN
- **Live** optimisation according to given costs by the user at runtime

Visions: Summary

Hybrid Models	• More complete reflection of the complexity of the problem • Increasing prediction accuracy
Prediction Interval	• Per-compound prediction uncertainty available • Freedom-of-choice for decision making • Individual selection of prediction value based on purpose
Cost-sensitive Models	• Live, objective accuracy- and cost-driven optimisation of a model for minimising FN or FP • Finally, the purpose of a QSAR prediction, the evaluation task it is used for, is driving the model result • Dealing with uncertainty of results